

**A STUDY ON INSULIN RESISTANCE AND OBESITY  
AMONG WOMEN AT HIGH RISK FOR BREAST  
CANCER USING CLUSTER ANALYSIS**

*Dissertation submitted to*

*The Tamil Nadu Dr. M. G. R. Medical University,  
Chennai*

*in partial fulfillment of the award of degree of*

**MASTER OF PHARMACY  
(PHARMACEUTICAL BIOTECHNOLOGY)**

*Submitted by*

**C. SHYNI MOLE.**

*Under the guidance of*

**Dr. D.C. SUNDARAVELAN, M. Pharm., Ph.D.**

**Department of Pharmaceutical Biotechnology**



**MARCH - 2010**

**COLLEGE OF PHARMACY**

**SRI RAMAKRISHNA INSTITUTE OF PARAMEDICAL SCIENCES**

COIMBATORE – 641 044.

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## *CERTIFICATE*

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Head,

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Coimbatore – 44

Place: Coimbatore

Date:

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***Dr. D.C. SUNDARAVELAN, M.Pharm., Ph.D.***

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Place: Coimbatore

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A Study on Insulin Resistance and Obesity among Women  
at High Risk for Breast Cancer Using Cluster Analysis

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## ABBREVIATIONS

|                |   |
|----------------|---|
| BMI            | Body mass index                                     |
| BFM            | Body Fat Mass                                       |
| DHEAS          | Dehydroepiandrosterone Sulphate                     |
| E <sub>1</sub> | Estrone   |
| E <sub>2</sub> | Estradiol   |
| FFAs           | Free fatty acids                                    |
| IGF-1          | Insulin-like growth factor                          |
| IGFBP-1/-2     | Insulin-like growth factor binding proteins 1 and 2 |
| IR             | Insulin Resistance                                  |
| IL-6           | Interleukin-6                                       |
| OGTT           | Oral Glucose Tolerance Test                         |
| PAR%           | population attributable risk                        |

|               |  |
|---------------|--|
| PPAR $\gamma$ | (Peroxisome Proliferative Activated<br>Receptor) |
| SHBG          | Sex hormone binding globulin                     |
| T             | Testosterone                                     |
| TNF $\alpha$  | Tumor necrosis factor $\alpha$                   |

## INTRODUCTION

Obesity, a chronic, relapsing, stigmatized, neurochemical disease that is more prevalent in developing/developed countries and leading to much comorbidity. Multiple factors are involved that contribute to the development of obesity. These may be social, behavioural, environmental and genetic. It is a global health problem in the present era.

## PATHOPHYSIOLOGY OF OBESITY

Obesity is characterized by an increase in subcutaneous adipose tissue. Its metabolic consequences, such as insulin resistance, are primarily attributable to increased fat deposition at sites such as the omentum, liver and skeletal muscles.

Recently, a virus has been found to be associated with obesity. Human adenovirus Ad-36 causes adiposity with obesity in animal models and enhances differentiation and lipid accumulation in human and 2T3-

L1 pre-adipocytes, which may, in part, explain the adipogenic effect of Ad-36 (Srivastava *et al.* 2007).

## **ROLE OF GENETICS IN OBESITY**

Genetics has shown tremendous effect on the process of weight gain. Recent genetic studies have identified several different causative mutations underlying such syndromes. The obesity gene map shows putative loci on all chromosomes except Y. Around 176 human obesity cases due to single-gene mutations in 11 different genes have been reported, 50 loci related to mendelian syndromes relevant to human obesity have been mapped to a genomic region, and causal genes or strong candidates have been identified for most of these syndromes.

Inherited forms of obesity are syndromic and are result of abnormal functioning of single genes leading to weight gain. About 30 mendelian disorders with obesity as a prominent feature, often are in association with mental retardation, dysmorphic features and organ-specific developmental abnormalities have been identified which include mainly – Prader-willi, Bardet-Biedl syndrome, Albright's hereditary osteodystrophy, Fragile X syndrome, Borjeson-Forssman-Lehmann Syndrome, Binge eating syndrome, Cohen syndrome, WAGR syndrome and Alstrom syndrome.

The more common forms of obesity are however polygenic. For most overweight people, obesity is a product of gene environment interaction.

### **INSULIN AND INSULIN RECEPTOR GENE**

Insulin substrate-1 gene occupies key position in insulin signaling pathway. After insulin binding to alpha subunit of insulin receptor, the beta subunit undergoes auto-phosphorylation and in turn phosphorylates other endogenous substrates in the cascade insulin action. Several polymorphisms have been identified in IRS-1 gene,



but Gly> Arg substitution at codon 972 is quite prevalent in Type II diabetes than in healthy controls. The polymorphism has been associated with impaired glucose tolerance, this association has been more marked in obese subject (BMI > 25 kg/m<sup>2</sup>).

## **ADIPONECTIN**

An adipocytokine encoded by APM1 gene localized on chromosome 3q27 is one of the adipocyte-expressed proteins which regulate the homeostatic control of glucose, lipid and energy metabolism. Evidences suggest its role in the genetic predisposition to metabolic X syndrome, such as insulin resistance, obesity, type 2 diabetes, and coronary artery disease. Adiponectin also enhances the transcription of other genes involved in fatty acid metabolism, most notably peroxisome proliferator-activated receptor- $\alpha$  (PPAR- $\alpha$ ). It also contains response elements for PPAR- $\gamma$ , a key regulator of glucose and lipid metabolism. Evidences also suggest that adiponectin secretion is modulated by interleukins which may modulate fat, lean body composition and insulin sensitivity.

## **RESISTIN**

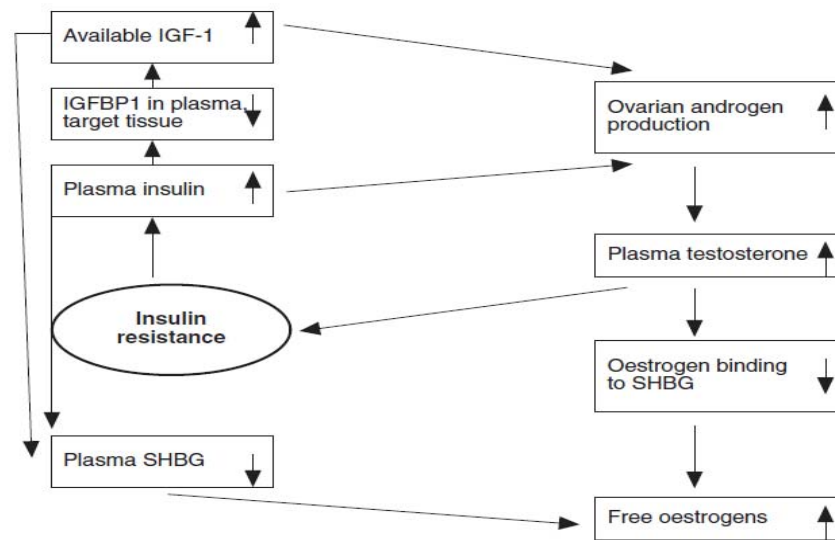
It is a cysteine-rich 12.5 kDa polypeptide, adipocytokine, with a controversial history regarding its role in pathogenesis of obesity-mediated insulin resistance and type 2 diabetes mellitus. The serum resistin concentration significantly correlates with the degree of obesity and distribution of fat.

## **OTHER CANDIDATE GENES**

The SLC6A14 gene is an interesting novel candidate for obesity. It encodes an amino acid transporter, which potentially regulates tryptophan availability for serotonin synthesis that possibly affects appetite control. Interleukin-1 receptor antagonist gene polymorphism has been found to be associated with higher BMI in north Indian population.

Berson and Yalow defined insulin resistance (IR) as a state (of a cell, tissue, system, or body) in which greater than normal amount of insulin is required to elicit a quantitatively normal response (Gupta *et al.* 2004). Resistance to insulin is an important risk factor in the industrial world and is often associated with obesity. Apart from its effect on the carbohydrate metabolism, insulin has diverse functions to perform in other body systems (Mohan, 2005).

Although insulin resistance is characterized by cells becoming less sensitive to the effects of insulin to transport glucose into cells, insulin insensitivity does not seem to lower the growth promoting properties of insulin. Only the glucose transporting properties are affected in insulin resistance. Thus, in an insulin resistant state, such as induced by obesity, the higher circulating levels of insulin may have a cancer-promoting influence for at least some tissues. As long as the pancreas can continue to produce large amounts of insulin in the face of insulin resistance, some individuals may avoid diabetes; however, these individuals may be the ones most susceptible to cancer because they have the highest circulating insulin concentrations.

**FIGURE 1**

Furthermore, obesity associated with increased incidence of type 2 diabetes mellitus, hypertension, coronary heart disease, arthritis, sleep apnea, and certain forms of cancer. Several obesity-related cancers, including breast, prostate, endometrium, colon and gallbladder cancer, have a hormonal basis and are life style-related. Breast cancer is the most frequent cancer and the second leading cause of cancer death among women. Excess adiposity over the pre- and post-menopausal years is an independent risk factor for the development of breast cancer, and is also associated with late-stage disease and poor prognosis (Yu Wang *et al.* 2007).

Breast cancer (BC) is one of the most important problem of public health. The inability to effectively predict, prevent, and treat metastatic breast cancer is a major problem in breast cancer care. One factor that may impact survival outcome is obesity (Lorincz *et al.* 2006). The risk of breast cancer is traditionally linked to obesity in postmenopausal women; conversely, it is neutral or even protective in premenopausal women. Since the initiator and promoter factors for breast cancer act over a long time, it seems unlikely that the menopausal transition may have too big an impact on the role of obesity in the magnitude of the risk.

### **POSSIBLE MECHANISMS OF BREAST CANCER RISK AND OBESITY**

- Reduced detection of tumour, late diagnosis
- Increased free bioactive estrogen levels\*
- Increased androgen levels\*
- Increased extraglandular conversion of androgens to estrogens
- Decreased steroid hormone binding globulin

- Increased growth factors (i.e. insulin-like growth factor\*)
  - Increased receptors for growth factors
  - Decreased specific binding proteins for growth factors
  - Hyperinsulinaemia
  - Increased insulin resistance
  - Elevated non-esterified fatty acids
  - Increased lipid-soluble carcinogens, especially in the breast\*
- \*- Mechanisms with direct involvement in mammary carcinogenesis

## **OBESITY AND ENDOGENOUS SEX STEROIDS**

Obesity has been associated with lower levels of sex hormone-binding globulin (SHBG) and plasma total and bioavailable androgens and estrogens. Sex steroids are mitogens that can stimulate cell proliferation, inhibit apoptosis, and therefore potentially increase the chance of malignant cell transformation, particularly of endometrium and breast but possibly also at other organ sites (eg, prostate-, colorectal cancer).

Several mechanisms may link obesity with the level of sex steroids. First, insulin and IGF-I stimulate the synthesis of sex steroids in ovarian, testicular or adrenal tissue, and

inhibit the hepatic synthesis of SHBG, increasing their free circulating levels and bioavailability to tissues. The increased production of androgen from the ovarian thecal cells and possibly from the adrenal gland leads to anovulatory cycles and lower progesterone levels. This syndrome, named polycystic ovary syndrome (PCOS), is a metabolic disorder also associated with insulin resistance. It has been related to a higher risk for endometrial cancer. Finally, adipocytes express sex hormone metabolising enzymes and are the main site of estrogen production in postmenopausal women. Obese women show higher aromatization of androgenic precursors to estrogens with BMI positively correlated with circulating sex-hormone levels (Ceschia *et al.* 2007).

As adipose tissue mass increases circulating concentrations of insulin and IGF-I, blood concentrations of SHBG begin to diminish. In one study, obese women (BMI >30 kg/m<sup>2</sup>) had an average SHBG concentration that was half that of women with a BMI of <22 kg/m<sup>2</sup> (McTiernan *et al.* 2003). SHBG binds testosterone and estradiol with high affinity. A decrease in SHBG in obesity results in an increase in the bioavailable fraction of circulating estradiol. In postmenopausal women, breast

cancer risk has been shown to be directly related to concentrations of various sex hormones, including estrone, total estradiol, and bioavailable estradiol, while blood levels of SHBG are inversely correlated with breast cancer risk (Jacquotte *et al.* 2004).

## POTENTIAL MECHANISMS FOR THE INFLUENCE OF TYPE 2 DIABETES ON THE RISK OF BREAST CANCER

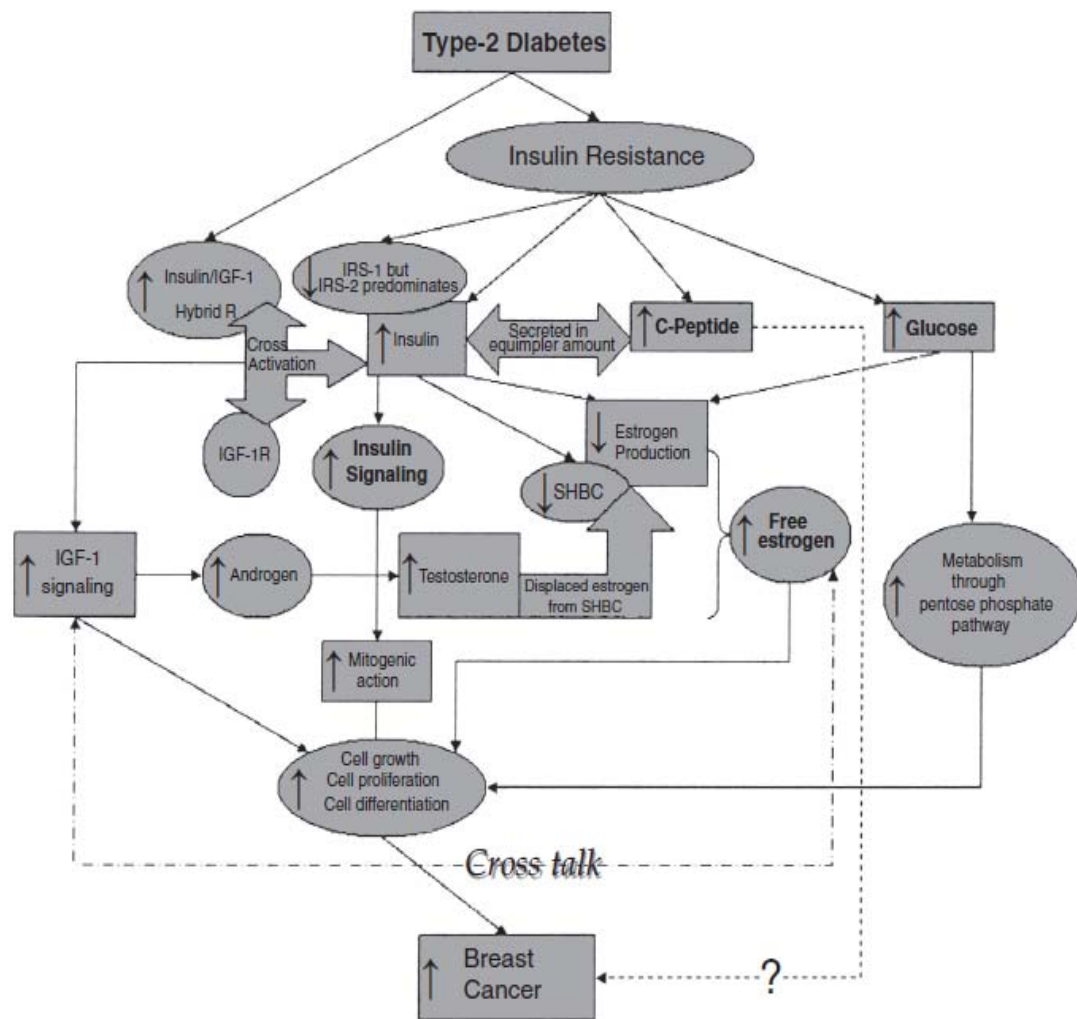
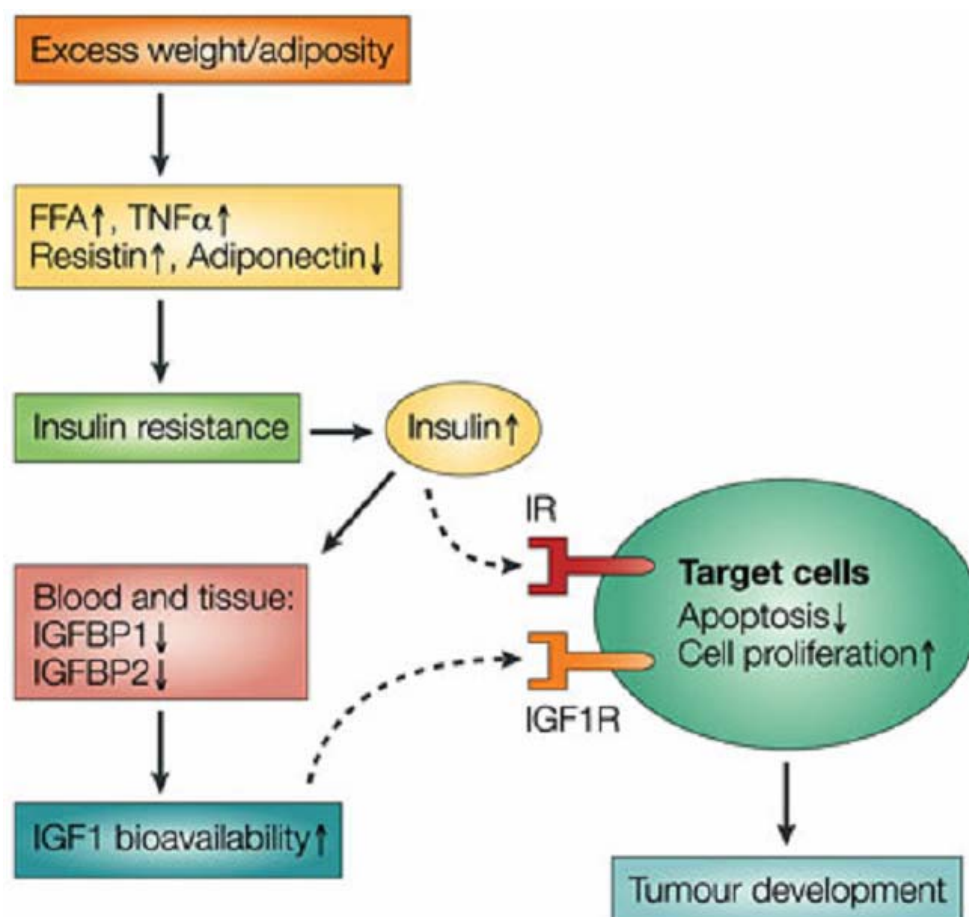




FIGURE 2

**OBESITY – CANCER****FIGURE 3**

In obesity, increased release from adipose tissue of free fatty acids (FFA), tumour-necrosis factor- (TNF) and resistin, and reduced release of adiponectin lead to the development of insulin resistance and compensatory, chronic hyperinsulinaemia. Increased insulin levels leads

to reduced liver synthesis and blood levels of IGFBP1.

Increased fasting levels of insulin in the plasma are generally also associated with reduced levels of IGFBP2 in the blood. This results in increased levels of bioavailable IGF1. Increased levels of serum IGF1 have been found to be related to increased risk of breast cancer, especially among premenopausal women. Insulin and IGF1 signal through the insulin receptors (IRs) and IGF1 receptor (IGF1R), respectively, to promote cellular proliferation and inhibit apoptosis in many tissue types. These effects might contribute to tumorigenesis.

## **OBESITY, HORMONES AND ENDOMETRIAL CANCER**

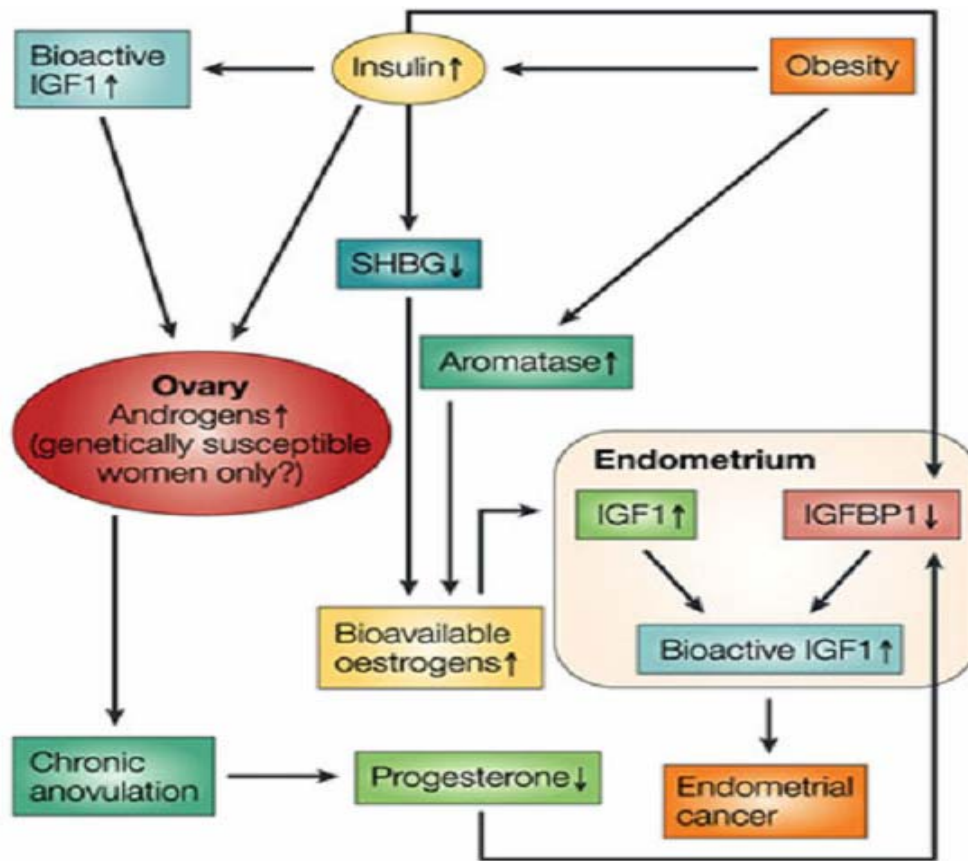


FIGURE 4

Obesity can increase the risk of endometrial cancer through several parallel endocrine pathways. Obesity is associated with increased insulin levels, which lead to increases in IGF1 activity and an increased androgen production by the ovaries. This inhibits ovulation (chronic anovulation), which leads to progesterone deficiency. Increased adiposity also increases aromatase activity, leading to increased levels of bioavailable estrogen levels in postmenopausal women. Estrogens increase

endometrial cell proliferation and inhibit apoptosis, partially by stimulating the local synthesis of IGF1 in endometrial tissue. Among premenopausal women, the lack of progesterone, because of ovarian androgen production and continuous anovulation, leads to reduced production of IGFBP1 by the endometrium. After menopause (and in the absence of exogenous estrogen production), when ovarian progesterone synthesis has ceased altogether, the more central risk factor seems to be obesity-related increases in bioavailable estrogen levels. In addition to estrogens and progesterone, insulin itself could also promote endometrial cancer development by reducing concentrations of sex-hormone-binding globulin (SHBG) in the blood, which would increase the levels of bioavailable estrogens that can diffuse into endometrial tissue.

Metabolic syndrome, also known as insulin resistance syndrome, consists of a cluster of conditions such as abdominal obesity, high blood glucose levels, impaired glucose tolerance, abnormal lipid levels and hypertension.

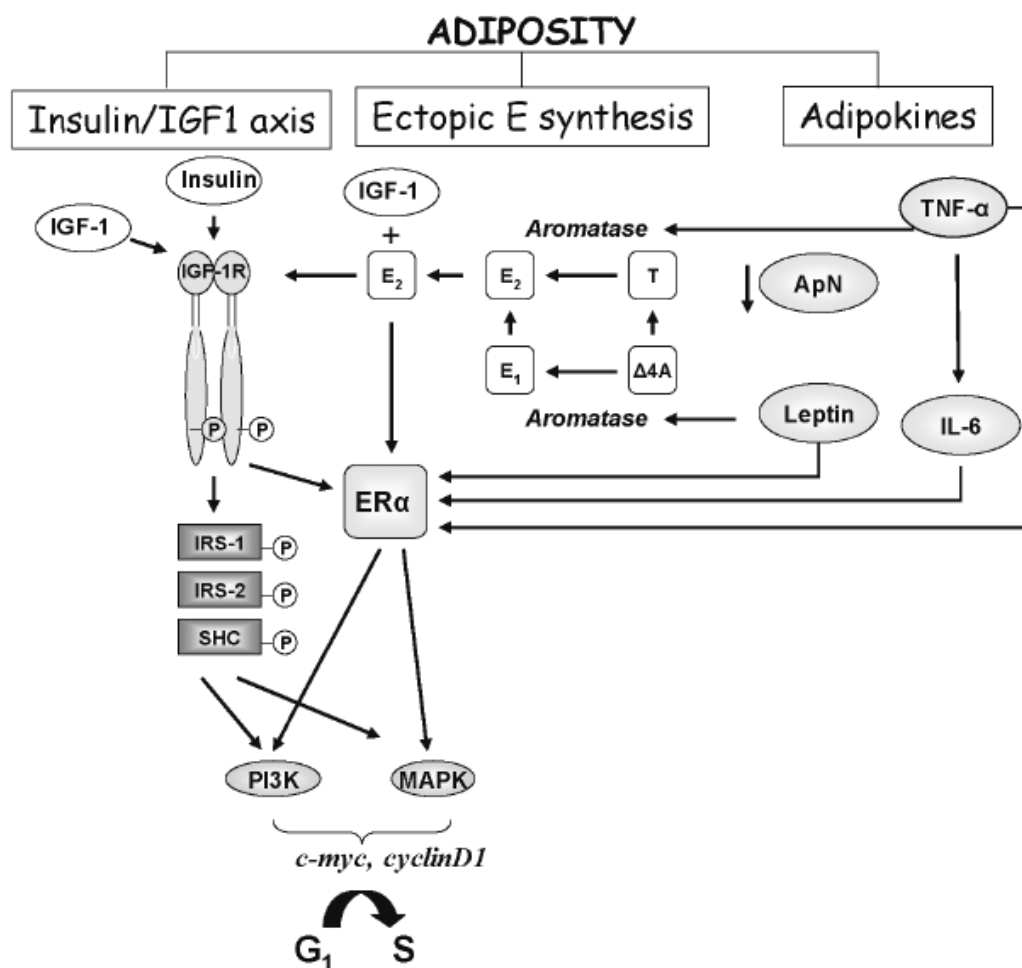
Obesity, type 2 diabetes and the metabolic syndrome also have in common an increased production of leptin and a decreased production of adiponectin by adipose tissue, with consequent

elevations and reductions, respectively, in the circulating levels of these two adipokines. Adiponectin is a key molecule mediating insulin resistance in obesity (Kadowaki *et al.* 2003). These changes in plasma leptin and adiponectin, acting through endocrine and paracrine mechanisms, have been associated in several studies with an increase in breast cancer risk and, to more aggressive tumours. Studies in vitro showed that leptin stimulates, and adiponectin inhibits, tumour cell proliferation and the microvessel angiogenesis which is essential for breast cancer development and progression (Davis et al (2007).

| S. NO | HORMONE OR BINDING GLOBULIN | OBESITY VS NORMAL WEIGHT  |
|-------|-----------------------------|---|
| 1     | Insulin                     | Increased levels with obesity   |
| 2     | IGF 1                       | Non-linear relation, with peak levels in people with BMI of 24-27 kg/m <sup>2</sup> . |
| 3     | Free IGF 1                  | Increased levels with obesity   |
| 4     | IGFBP1                      | Decreased levels with obesity   |
| 5     | IGFBP3                      | Increased levels with obesity   |
| 6     | SHBG                        | Decreased levels with obesity   |
| 7     | Total testosterone          | Increased levels with obesity (premenopausal women with PCOS)                         |
| 8     | Free testosterone           | Increased levels with obesity   |
| 9     | Total estradiol             | Increased with obesity in postmenopausal women  |
| 10    | Free estradiol              | Increased levels with obesity in postmenopausal women                                 |

|    |              |   |
|----|--------------|---|
| 11 | Progesterone | In premenopausal – decreased levels with obesity with a susceptibility to develop ovarian hyperandrogenism. |
|----|--------------|---|

## **MOLECULAR MECHANISMS SUPPORTING THE LINK BETWEEN OBESITY AND BREAST CANCER**

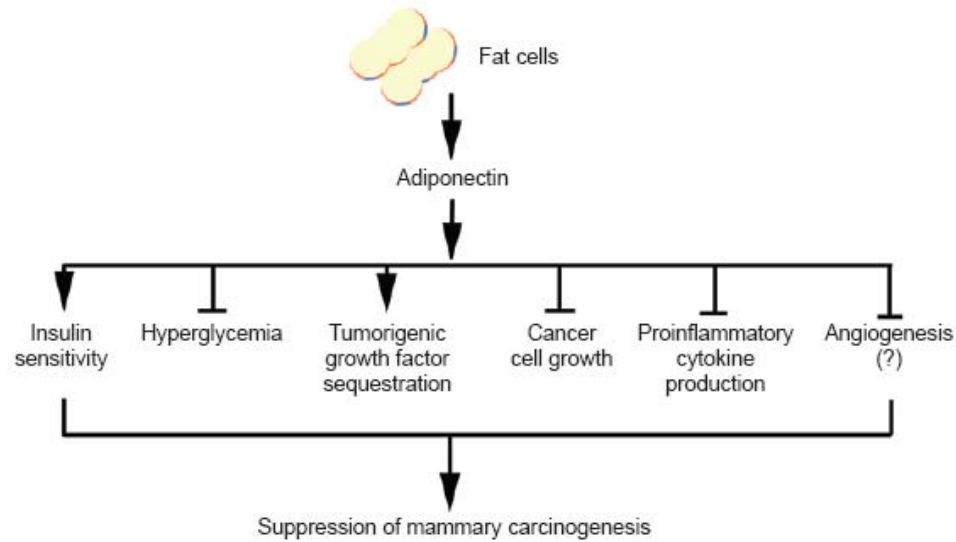
**FIGURE 5**

Three mechanisms are thought to contribute to the association between type 2 diabetes and breast cancer: activation of the insulin pathway, activation of the insulin-like-growth-factor pathway, and impaired regulation of endogenous sex hormones (Ido Wolf *et al.* 2005).

Adipose tissue has been shown to be an important player in obesity-related mammary carcinogenesis.



Adiponectin suppresses obesity-related mammary tumorigenesis via multiple mechanisms:



**FIGURE 6**

Adipocyte is one of the predominant stromal cell types in the microenvironment of mammary tissue. It is also the major site for local estrogen production from androgens by aromatase, thus contributing to the development of estrogen-dependent breast cancer in postmenopausal women. Low levels of adiponectin in insulin resistance suggest that therapeutic modulation of adiponectin may provide a novel treatment for insulin resistance as well (Kaur *et al.* 2005). Additionally, the increased fat mass is associated with aberrant insulin

signaling (insulin resistance) and increased insulin levels, which could directly stimulate mammary carcinogenesis.

## **INCREASED ESTROGEN IN OBESE POSTMENOPAUSAL WOMEN**

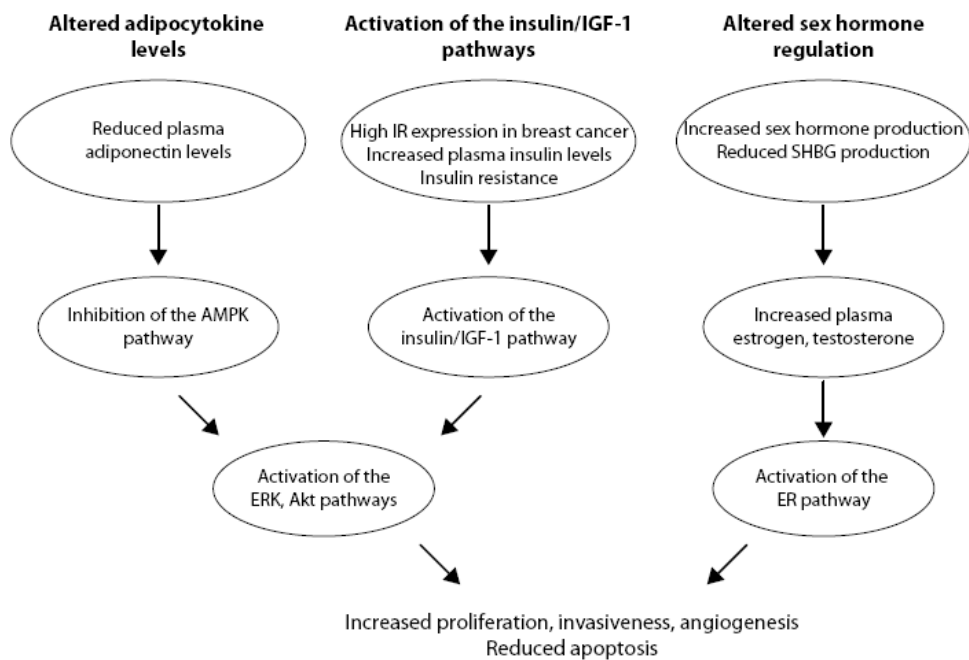
In obese post-menopausal women, adipose tissue of the breast, abdomen, thighs, and buttocks are the main sites of estrogen biosynthesis, with levels of aromatase increasing with age and BMI. In fact, local estrogen levels in breast tumors are as much as 10 times greater than in the circulation of postmenopausal women. This is presumably due to tumor–adipocyte interactions that stimulate the increased production of aromatase. Other factors, such as tumor necrosis factor  $\alpha$  (TNF- $\alpha$ ) and interleukin (IL)-6, are secreted by adipocytes and act in an autocrine or paracrine manner to stimulate production of aromatase.

Insulin resistance leads to high plasma insulin concentrations, which activate the extracellular-related-kinase (ERK) and the AKT pathways through activation of the insulin receptor (IR) or the insulin-like-growth-factor-1 (IGF-1) receptor. High expression of the insulin receptor in

breast cancer augments activation of these pathways. Diabetes is associated with reduced adiponectin plasma levels, which inhibits the AMP kinase (AMPK) and activates the ERK and Akt pathways in breast cancer cells. Diabetes increases production of sex

hormones and decreases sex hormone binding globulin (SHBG) production, leading to high plasma free estrogen concentrations, which in turn activate the estrogen receptor (ER). Activation of these

pathways can lead to proliferation, invasiveness, angiogenesis and decreased apoptosis (Ido Wolf *et al.* 2008).



**FIGURE 7**

The link between the insulin resistance hormones, IGF-I, IGFBP-3 and C-peptide, a positive energy balance, and breast cancer risk is that higher levels of visceral fat result in a compensatory response of resistance to the insulin-stimulated glucose uptake in the peripheral tissues. The overabundance of insulin, called hyperinsulinemia, amplifies the bioavailability of IGF-I. IGFI and insulin together have been shown to stimulate motility in human breast cancer cell lines (Alecia Malin Fair *et al.* 2007).

**OBESITY AND BODY FAT DISTRIBUTION**

Obesity and body fat distribution are major determinants of sex hormone-binding globulin (SHBG). The sex hormone-binding globulin levels decrease substantially with increasing levels of obesity among postmenopausal women. The degree of obesity, the amount of intra-abdominal fat, and the waist-to-hip ratio have all been related to the increased risk of breast cancer. The levels of SHBG and any relationship to breast cancer may, therefore, be only a measure of the degree of obesity and the high correlation with levels of sex hormone-binding globulin.

**FAT DISTRIBUTION, SEX HORMONES AND BREAST CANCER RISK**

Hormone levels are greatly influenced not only by total fat mass but more significantly by fat distribution. The decreased synthesis of SHBG in overweight and obese women is predominantly linked to visceral obesity and associated with hyperinsulinaemia. In post-menopausal women the incidence of obesity increases and is often centrally distributed. This is in turn linked to higher levels of estrogens produced from androgens in the adipocyte and decreased estrogen–protein binding due to the reduction in SHBG, leading to higher bioavailable estrone and 17- $\beta$ -estradiol. Increased levels of bioavailable androgens are also linked to a central fat distribution and increase breast cancer risk directly through increasing breast cancer cell proliferation after binding to androgen receptors, in addition to their influence on insulin sensitivity. There is also strong evidence that insulin is the central regulating factor for hepatic SHBG production and has been shown to inhibit the production of SHBG in liver cells. There is also relatively strong evidence that elevated plasma concentrations of insulin are related to lower SHBG levels in obese women.

The severity of obesity is estimated from the total amount of fat and the fat distribution in the human body. In clinical practice, more simple methods are used, such as the weight - height tables, the Body Mass Index (BMI) assessment and the skin fold measurement. The weight - height tables, which are published in many different versions, indicate an acceptable weight range for a

particular height, different between men and women, beyond which, a person is defined as either underweight or overweight. The main disadvantage in using them, is the fact that it is not possible to distinguish between fat and muscle percentage. Consequently, a very muscular person is possible to be described by such a table as obese.

The body mass index (BMI), or Quetelet index, is a controversial statistical measurement which compares a person's weight and height. BMI is a very common, easy and reliable way to classify patients into groups and compare them. Although there is a high correlation between BMI and fat percentage, it does not provide information about the weight of the muscle tissue and bones. BMI is a mathematical formula that is defined by dividing the body weight to the second power of the height:

$$\text{BMI} = \text{Body Weight (Kg)} / \text{height}^2 (\text{m}^2)$$

## **BODY FAT MASS**

Skin- fold measurements technique is the simplest method for measuring body fat percentage and the results are obtained according to specific tables. Waist Circumference (WC) provides important information about the accumulation and distribution of the body fat. More specifically, it is considered an adequate tool for assessing central obesity. Also, the ratio of Waist to Hip (WHR) is another easy method for assessing central obesity. WHR is defined as the ratio between the lower part of the crest of the iliac ala and the perimeter of the hips, measured at the level of trochanters.

$$\text{Body fat \%} = \frac{\text{BFW}}{\text{TBW}} \times 100$$

**TBW**

$$\text{Body fat weight (BFW)} = \text{TBW} - \text{LBM}$$

$$\text{LBM} = \text{Factor 1} + ((\text{factor 2} + \text{factor 5}) - (\text{factor 3} + \text{factor 4}))$$

$$\text{Factor 1} = \text{TBW} \times 0.732 + 8.987$$

$$\text{Factor 2} = \frac{\text{Wrist circumference}}{3.140}$$

3.140

$$\text{Factor 3} = \text{Waist circumference} \times 0.157$$

Factor 4 = Hip circumference x 0.249

Factor 5 = Forearm circumference x 0.434

### **APPLICATIONS:**

1. BMI is also used as a measure of underweight, owing to advocacy on behalf of those suffering with eating disorders, such as anorexia nervosa and bulimia nervosa
2. BMI can be calculated quickly and without expensive equipment.

### **LIMITATIONS:**

1. Because the BMI is dependent only upon weight and height, it makes simplistic assumptions about distribution of muscle and bone mass, and thus may overestimate adiposity on those with more lean body mass (e.g. athletes) while underestimating adiposity on those with less lean body mass (e.g. the elderly).



2. Loss of height through aging. In this situation, BMI will increase without any corresponding increase in weight.

## **MEASUREMENT OF INSULIN RESPONSE**

The gold standard for measuring hyperinsulinemic clamp technique, while that for measuring the response of  $\beta$ -cell to glucose is the hyperglycemic clamp technique. However, such complicated and time consuming procedures are not convenient for clinical use and thus more simple methods are recommended for epidemiological studies.

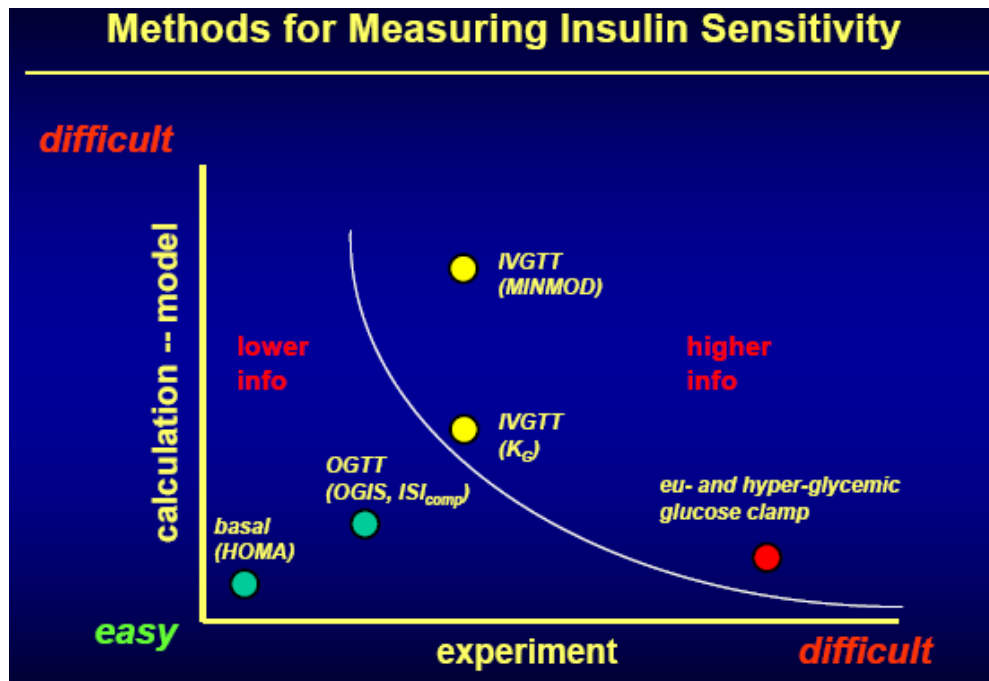


FIGURE 8

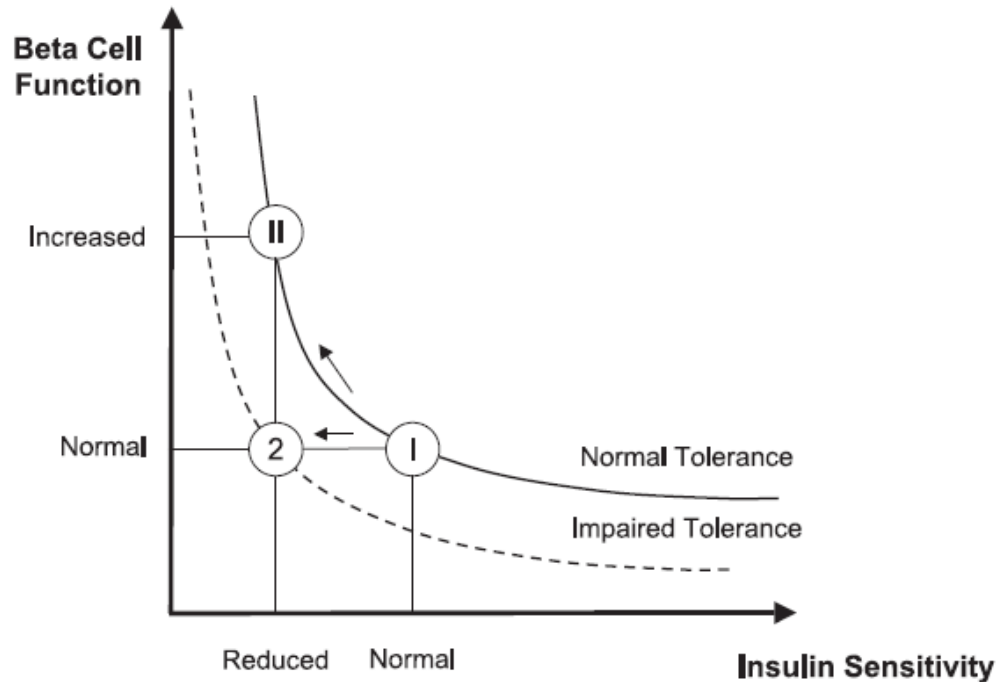
The oral glucose tolerance test (OGTT) recommended by WHO is the most widely used for estimation of whole-body glucose tolerance *in vivo*. However, a large number of subjects with normal glucose levels during OGTT shows abnormal insulin sensitivity. To predict the risk of development of insulin resistance and type 2 diabetes mellitus in such subjects, several insulin sensitivity indices as calculated from plasma glucose and plasma insulin concentrations during OGTT were proposed. The values correlated closely with the insulin sensitivity as defined by the euglycemic clamp method (Cervenakova *et al.* 2002).

In this study, various insulin sensitivity indices derived from the concentrations of insulin and glucose during fasting state and during OGTT in subjects with normal glucose tolerance were calculated and compared with respect to their relationship with body mass.

The major role of the insulin sensitivity indices are

1. To predict the development of diabetes mellitus Type 2 in healthy population and in individuals with impaired glucose metabolism.
2. To assess the degree of insulin sensitivity in non-diabetic population with risk factors present.

## DISPOSITION INDEX



**GRAPH 1**

The importance of expressing  $\beta$ -cell responsiveness in relation to insulin sensitivity is illustrated by using the disposition index metric; i.e., the product of  $\beta$ -cell responsiveness and insulin sensitivity is assumed to be a constant. A normal subject reacts to impaired insulin sensitivity by increasing  $\beta$ -cell responsiveness (state II), whereas a subject with impaired tolerance does not (state 2). In state II,  $\beta$ -cell responsiveness is increased but the disposition index  $\beta$ -cell metric is normal, whereas in state

2,  $\beta$ -cell responsivity is normal but the disposition index is impaired.

## HOMEOSTASIS MODEL (HOMA)

The homeostasis model assessment (HOMA) represents the simplest model for evaluating insulin sensitivity and secretion. This model was based on the assumption that normal-weight healthy subjects aged < 35 years have an insulin resistance of 1 and  $\beta$ -cell function of 100%. HOMA calculates insulin resistance and  $\beta$ -cell function from fasting glucose (nmol/l) and insulin (mIU/l) concentrations. The formulas represent an approximation to the HOMA, where  $IR_{HOMA}$  stays for the insulin resistance.

$$IR_{HOMA} = \frac{I_0 \times G_0}{22.5}$$

**22.5**

The ability to easily assess insulin sensitivity would therefore be useful for investigating the role of insulin

resistance in the pathophysiology of these diseases (Soonthornpun *et al.* 2002).

Homeostasis model assessment (HOMA) proposed by Matthews *et al.* (1985) is based on the relationship between insulin and glucose concentrations during fasting state. The  $IR_{HOMA}$  correlated well with insulin resistance as measured by euglycemic clamp.

## CEDERHOLM INDEX

The insulin sensitivity index proposed by Cederholm and Wibell (1990) represents mainly peripheral insulin sensitivity and muscular glucose uptake, due to the dominant role of peripheral tissues in glucose disposal after an oral glucose load.

$$ISI_{Cederholm} = \frac{75000 + (G_0 - G_{120}) \times 1.15 \times 180 \times 0.19 \times BW}{120 \times \log(I_{mean}) \times G_{mean}}$$

Where 75000 - oral glucose load in an OGTT (75000 mg)

$G_0$  - fasting plasma glucose concentration (mmol/l)

$G_{120}$  - plasma glucose concentration in the 120 min of OGTT (mmol/l)

1.15 - factor transforming whole venous blood glucose to plasma values

180 - conversion factor to transform plasma glucose concentration from mmol/l into mg/l.

0.19 - glucose space in liter per kg of body weight

BW - body weight (kg)

$I_{\text{mean}}$  - mean plasma insulin concentration during OGTT (mU/l)

$G_{\text{mean}}$  - mean glucose concentration during OGTT (mmol/l)

## GUTT INDEX

This index was adapted from the insulin sensitivity index proposed by Cederholm and Wibell (1990). It is expressed in  $\text{mg.l}^2.\text{mmol}^{-1}.\text{mIU}^{-1}.\text{min}^{-1}$ .

$$\text{ISI}_{0,120} = \frac{75000 + (G_0 - G_{120}) \times 0.19 \times \text{BW}}{120 \times G_{\text{mean}} \times \log(I_{\text{mean}})}$$

Where 75000 - oral glucose load in an OGTT (75000 mg)

$G_0$  - fasting plasma glucose concentration (mmol/l)

$G_{120}$  - plasma glucose concentration in the 120 min of OGTT (mmol/l)

0.19 - glucose space in liter per kg of body weight

BW - body weight (kg)

$I_{\text{mean}}$  - mean plasma insulin concentration during OGTT (mIU/l)

$G_{\text{mean}}$  - mean glucose concentration during OGTT (mmol/l)



## STUMVOLL INDEX

Stumvoll *et al.* proposed a series of indices calculated from plasma glucose and insulin concentrations during OGTT. The equations were generated using the multiple linear regression analysis and adapted to the availabilities of sampling times during OGTT and demographic parameters (BMI, age).

$$\text{ISI}_{\text{Stumvoll}} = 0.222 - 0.00333 \times \text{BMI} - 0.0000779 \times \text{I}_{120} - 0.000422 \times \text{Age}$$

BMI - Body mass index (kg/m<sup>2</sup>)

In the overweight group the insulin sensitivity indices were lower  $\text{ISI}_{\text{Stumvoll}}$ ,  $\text{ISI}_{\text{Cederholm}}$ ,  $\text{ISI}_{\text{Matsuda}}$  and insulin resistance index  $\text{IR}_{\text{HOMA}}$  was higher. BMI correlated inversely with insulin sensitivity indices and the correlation was highest in  $\text{ISI}_{\text{Matsuda}}$ , followed by  $\text{ISI}_{\text{Cederholm}}$  and  $\text{ISI}_{\text{Stumvoll}}$ . The indices of insulin secretion were in positive relationship with BMI and the  $\text{AUC}_{\text{ins}}$  showed better correlation than  $\text{Secr}_{\text{HOMA}}$ .



















**ADVANTAGES:**

There are many mathematical models to detect insulin resistance or insulin sensitivity. It would be helpful if one can evaluate insulin resistance or sensitivity in a clinical setting. This can help select the most appropriate candidates for insulin-sensitising drugs and subsequent planning of interventions.

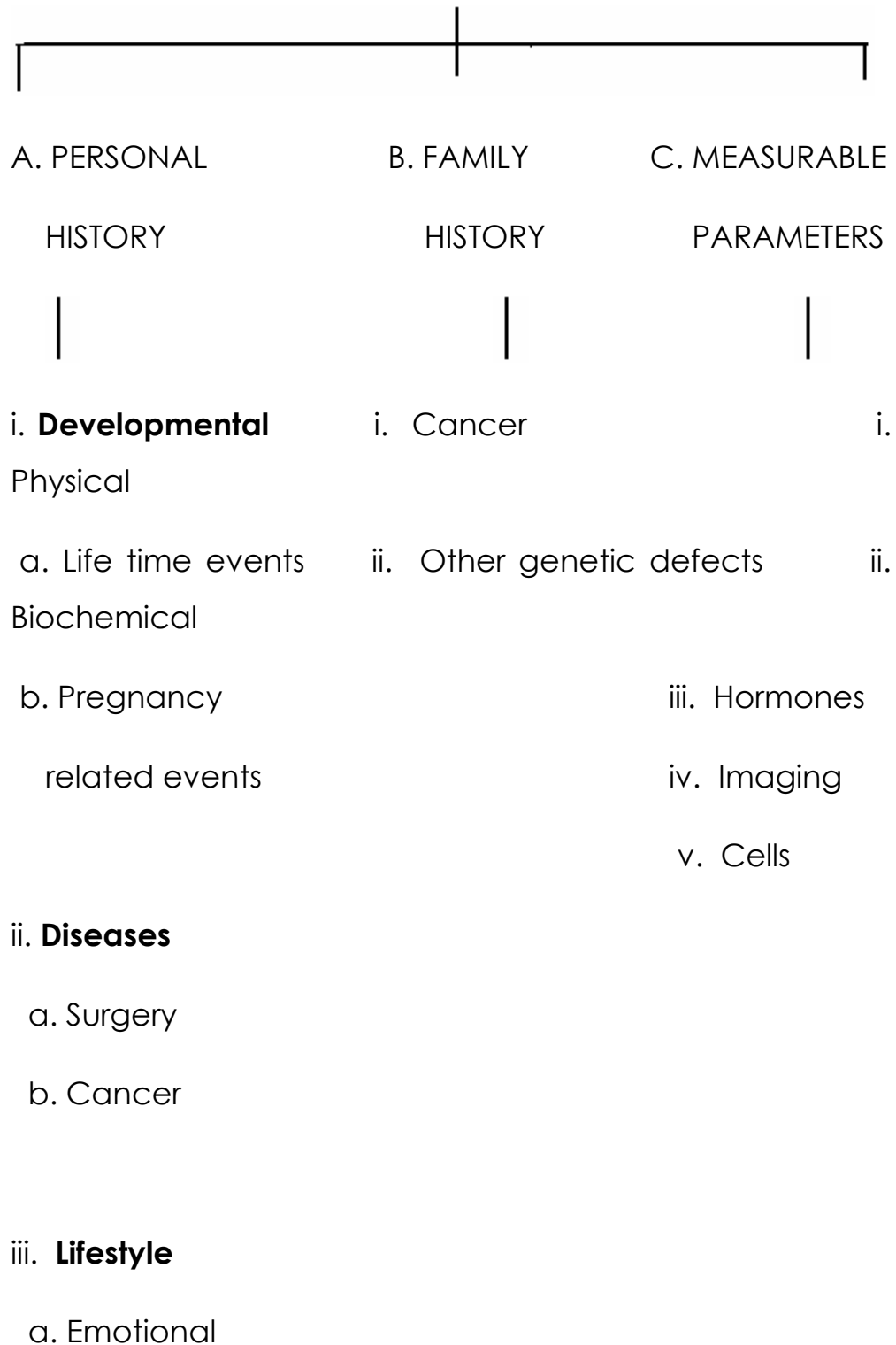
**EQUATIONS OF INSULIN SENSITIVITY INDICES**

| S.NO | INDEX                                     | EQUATION      |
|------|---|---------------|
| 1    | FASTING<br>INSULIN <sup>-1</sup>          | $1/INS_0$     |
| 2    | FASTING<br>GLUCOSE<br>TO INSULIN<br>RATIO | $GLU_0/INS_0$ |
| 3    | HOMA IR                                   | $IG/22.5$     |

|    |                      |  |
|----|----------------------|--|
| 4  | RAYNAUD              | $40/INS_0$   |
| 5  | BELFOIRE(F)          | $2/IG+1$   |
| 6  | FIRI-1               | $1/I \times G/22.5$  |
| 7  | QUICKI               | $1/LOG I /LOG G$   |
| 8  | INS120 <sup>-1</sup> | $1/INS_{120}$  |
| 9  | CEDERHOLM            | $\frac{75000 + (\text{fasting glucose} - 2\text{-h glucose}) \times 1.15 \times 180 \times 0.19 \times BW}{120 \times \log(\text{mean insulin}) \times \text{mean glucose}}$ |
| 10 | MATSUDA              | $\frac{10,000}{\sqrt{(\text{fasting glucose} \times \text{fasting insulin}) \times (\text{mean glucose} \times \text{mean insulin})}}$                                       |
| 11 | GUTT                 | $\frac{75000 + (G_0 - G_{120}) \times 0.19 \times BW}{120 \times G_{\text{mean}} \times \log(I_{\text{mean}})}$  |
| 12 | Stumvoll             | $0.22 - 0.0032 \times BMI - 0.0000645 \times 2\text{-h insulin} - 0.0037 \times 1.5\text{-h glucose}$  |

| Component      | Association with obesity  | Association with breast cancer  | Primary source  |
|----------------|---|---|---|
| PAI-1          |    |   | Breast epithelial cells, endothelial cells, smooth muscle cells, adipocytes |
| uPA            | Unknown   |   | Tumor cells, epithelial cells   |
| uPAR           | Unknown   |    | Monocytes, neutrophils, epithelial cells, tumor cells                       |
| TNF- $\alpha$  |    |    | Macrophages, adipocytes, lymphocytes  |
| Aromatase      |    |    | Breast epithelium, endometrium, adipocytes                                  |
| Leptin         |   |   | Adipocytes  |
| Adiponectin    |  |  | Adipocytes  |
| PPAR- $\gamma$ |  |  | Adipocytes, tumor cells   |
| $\omega$ -3 FA |  |  | Diet  |
| $\omega$ -6 FA |  |  | Diet  |

## RISK FACTORS FOR BREAST CANCER



b. Behavioural

c. Work-related

## **A. PERSONAL HISTORY**

i. Developmental

ii. Diseases

iii. Lifestyle

a. Lifetime events

a. Surgery

a. Emotional

1. Age at menarche

1. Biopsies

1. Stress

2. Age at first live birth

2. Radiation exposure

2.

Personality

3. Age at menopause

3. HRT

4. Parity/ Nulliparity

b. Pregnancy related

b. Cancer

b.

Behavioural

- i. Nausea/vomitting
- ii. Induced abortion
- Alcohol
- iii. GDM
- iv. Weight gain
- v. Pre-eclampsia
- vi. High birth weight
- vii. Synthetic estrogens
- i. Ovarian
- ii. Pancreatic
- iii. ADH
- iv. ALH
- v. LCIS
- i. Smoking
- ii.
- c. Work-related
- i. Type of occupation

## **B. FAMILY HISTORY**

- i. Cancer
- ii. Other genetic defects
- 1. No of cancer cases
- 2. Relationship (1°, 2°, 3°)
- 3. Age at cancer

## **C. MEASURABLE PARAMETERS**

a. Physical

1. BMI → Height, weight
2. Waist circumference
3. Hip circumference
4. WHR
5. Wrist circumference
6. Forearm circumference
7. Percent body fat

b. Biochemical

1. Aromatase
2. POMC peptides
3. IL-6
4. IL-1  $\beta$
5. Lipids/ triglycerides/ cholesterol
6. Tumour- infiltrating lymphocytes
7. Adiponectin
8. Insulin
9. IGF-1
- 10.IGF-2
- 11.Leptin



12.C-peptide

13.IGFBP-3

14.NEFA

15.Fructosamine

c. Hormones

1. Estradiol-free E<sub>2</sub>, non- SHBG bound E<sub>2</sub>, SHBG bound E<sub>2</sub>,  
total E<sub>2</sub>

2. Estrone

3. Estriol

4. SHBG (↓)

5. Testosterone- free T

6. DHEA (S)

7. Androsterone (↓)

8. Etiocholanolone (↓)

9. Androstenedione

10. Prolactin

11. LH

12. FSH

13. Progesterone

14. CBG

c. Imaging

1. Mammogram
2. MRI
3. Elastography
4. Breast ultrasound
5. Ductogram
6. Scinti-mammography
7. Tomosynthesis

e. Cells

1. Breast cells
2. Bone Mineral Density
3. Breast density

## **DRUGS FOR BREAST CANCER TREATMENT**

### **ANDROGENS**

Calustserone    Epitiostanol                      Testolactone  
                    Testosterone Propionate  
Dromostanolone              Mepitiostane

### **ANTIADRENALS**

Aminoglutethimide    Exemestane                      Formestane  
Vorozole

### **ANTI-ESTROGENS**

Droloxifene                      Tamoxifen                      Toremifene  
Exemestane

### **ANTIPROGESTINS**

Onapristone

### **AROMATASE INHIBITORS**

Aminogluethimide                      Exemestane  
Formestane                      Vorozole  
Anastrozole                      Fadrozole                      Letrozole  
Acolbifene

### **ESTROGENS**

Diethylstilbestrol Hexestrol    Estradiol    Ethinylestradiol  
Fosfestrol    Polystradiol PO<sub>4</sub>

### **LH-RH ANALOGS**

Buserilin    Goserilin            Triptorelin    Cetorelix

### **PROGESTOGENS**

Chlormadinone Medroxy    Megestrol Acetate

Melengesterol

Acetate            Progesterone Hydroxyprogesterone

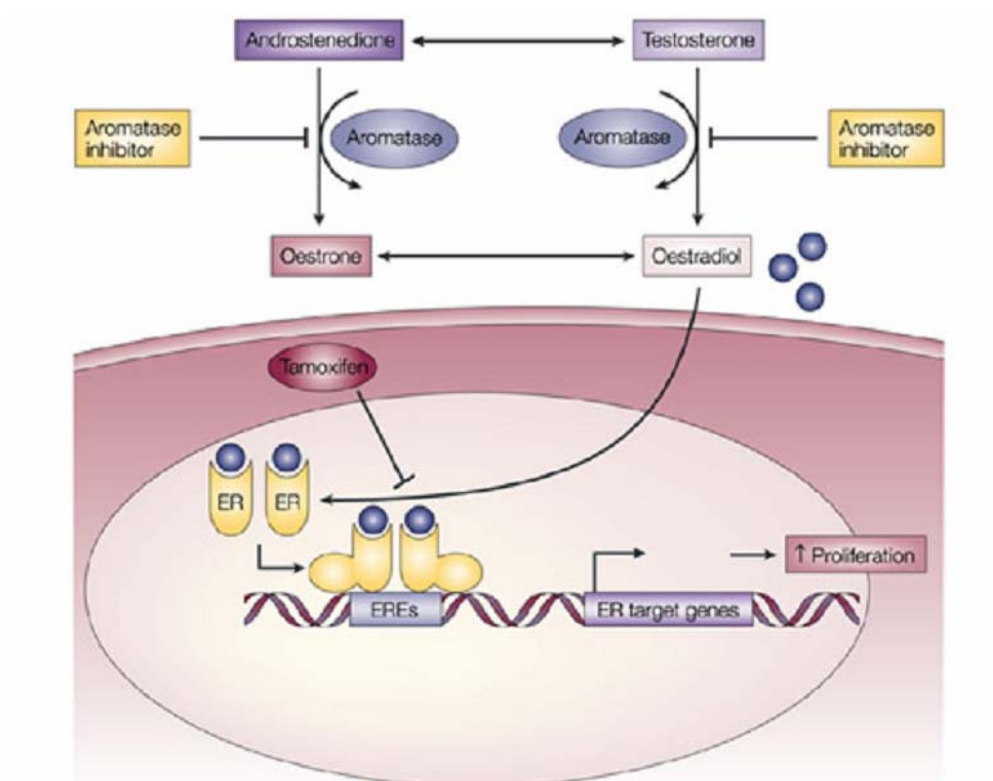
### **MONOCLONAL ANTIBODIES**

Herceptin

### **AROMATASE INHIBITORS:**

There are two types of aromatase inhibitors namely

1. Irreversible steroidal activators and
2. Reversible nonsteroidal imidazole-based inhibitors.

**FIGURE 9**

Breast cancer cell growth may be estrogen-dependent. Aromatase is the principal enzyme that

converts androgens to estrogens both in pre- and postmenopausal women. While the main source of estrogen (primarily estradiol) is the ovary in premenopausal women, the principal source of circulating estrogens in postmenopausal women is from conversion of adrenal and ovarian androgens (androstenedione and testosterone) to estrogens (estrone and estradiol) by the aromatase enzyme in peripheral tissues. Estrogen deprivation through aromatase inhibition is an effective and selective treatment for some postmenopausal patients with hormone-dependent breast cancer.

## **AROMATASE INHIBITORS**

### **EXEMESTANE**

**Mechanism of Action:** Exemestane is an irreversible, steroidal aromatase inactivator, structurally related to the natural substrate androstenedione. It acts as a false substrate for the aromatase enzyme, and is processed to an intermediate that binds irreversibly to the active site of the enzyme causing its inactivation, an effect also known as "suicide inhibition." Exemestane significantly lowers circulating estrogen concentrations in

postmenopausal women, but has no detectable effect on adrenal biosynthesis of corticosteroids or aldosterone. Exemestane has no effect on other enzymes involved in the steroidogenic pathway up to a concentration at least 600 times higher than that inhibiting the aromatase enzyme.

**SIDE EFFECTS:** Hot flashes, nausea, fatigue, increased appetite, joint pain and muscle pain, hair loss, hypertension, insomnia, increased sweating, vision problems, arm or leg pain. back pain, arthritis, dizziness, abdominal pain (or stomach pain), diarrhea, flu symptoms (such as fever or chills), swelling or water retention, constipation.

## **LETROZOLE**

**MECHANISM OF ACTION:** Letrozole is a non-steroidal competitive inhibitor of the aromatase enzyme system; it inhibits the conversion of androgens to estrogens.



Letrozole selectively inhibits gonadal steroidogenesis but has no significant effect on adrenal mineralocorticoid or glucocorticoid synthesis. Letrozole inhibits the aromatase enzyme by competitively binding to the heme of the cytochrome P450 subunit of the enzyme, resulting in a reduction of estrogen biosynthesis in all tissues. Treatment of women with letrozole significantly lowers serum estrone, estradiol and estrone sulfate and has not been shown to significantly affect adrenal corticosteroid synthesis, aldosterone synthesis, or synthesis of thyroid hormones.

**SIDE EFFECTS:** Musculoskeletal pain, nausea, head ache, joint pain, fatigue, difficulty in breathing, muscle pain, constipation, diarrhea, drowsiness and joint pain

## **ANASTROZOLE**

**MECHANISM OF ACTION:** Anastrozole is a potent and selective non-steroidal aromatase inhibitor. It significantly lowers serum estradiol concentrations and has no detectable effect on formation of adrenal corticosteroids or aldosterone

**SIDE EFFECTS:** Hot Flashes, asthenia, arthritis, pain, arthralgia, pharyngitis, hypertension, depression, nausea and vomiting, rash, osteoporosis, fractures, back pain, insomnia, pain, headache, bone pain, peripheral edema, increased cough, dyspnea, pharyngitis and lymphedema.

## **AMINOGLUTETHIMIDE**

**MECHANISM OF ACTION:** It inhibits the enzymatic conversion of cholesterol to  $\Delta^5$ -pregnenolone, resulting in a decrease in the production of adrenal glucocorticoids, mineralocorticoids, estrogens, and androgens and blocks several other steps in steroid synthesis, including the C-11, C-18, and C-21 hydroxylations and the hydroxylations required for the aromatization of androgens to estrogens, mediated through the binding of aminoglutethimide to cytochrome P-450 complexes.

**SIDE EFFECTS:** The most frequent and reversible side effects were drowsiness, morbilliform skin rash, nausea and anorexia, and dizziness. The dizziness was possibly caused by lowered vascular resistance or orthostasis.

## ANDROGENS

### TESTOLACTONE

**Mechanism of Action:** Inhibition of steroid aromatase activity and consequent reduction in estrone synthesis from adrenal androstenedione, the major source of estrogen in postmenopausal women. Based on *in vitro* studies, the aromatase inhibition may be noncompetitive and irreversible.

**Side Effects:** Maculopapular erythema, increase in blood pressure, paresthesia, malaise, aches and edema of the extremities, glossitis, anorexia, and nausea and vomiting. Alopecia alone and with associated nail growth disturbance have been reported rarely; these side effects subsided without interruption of treatment.

## **ANTI-ESTROGENS**

### **FARNESTON**

**MECHANISM OF ACTION:** Binds to estrogen receptors on breast cancer cells, preventing the cells from growing and dividing.

**SIDE EFFECTS:** Hot flashes, nausea, weight gain, allergic reactions like skin rashes and headache.

### **FULVESTRANT:**

**MECHANISM OF ACTION:** Fulvestrant is an estrogen receptor antagonist that binds to the estrogen receptor in a competitive manner with affinity comparable to that of estradiol. It downregulates the ER protein in human breast cancer cells. It exerts its action by blocking the binding of estrogens to the estrogen receptor in all tissues, thereby causing generalized estrogen deprivation.

**SIDE EFFECTS:** Gastrointestinal symptoms (including nausea, vomiting, constipation, diarrhea and abdominal pain), headache, back pain, vasodilatation (hot flushes), and pharyngitis.

## **MONOCLONAL ANTIBODIES**

### **HERCEPTIN**

**MECHANISM OF ACTION:** Herceptin attaches to the protein receptor on the surface of breast cancer cells. By binding to the cells, herceptin slows the growth and spread of tumors that have an overabundance of HER2 protein receptors.

**SIDE EFFECTS:** Weakening of the heart muscle, reduction of white blood cells, diarrhea, anemia and abdominal pain or infection.

### **MEGESTROL**

**MECHANISM OF ACTION:** Pharmacologic doses of megestrol exerted a direct cytotoxic effect on human breast cancer cells in vitro and proved capable of modifying and abolishing the stimulatory effects of estrogen on breast cancer cell lines. Megestrol interacts with progesterone receptors to stimulate cell maturation through a progestin-inducing mechanism. It has also been shown to have certain androgenic properties and may also modify glucocorticoid action by binding to the glucocorticoid receptor.

**SIDE EFFECTS:** Changes in appetite, thirst or weight, diarrhea, constipation, frequent urination, swelling of ankles or feet, increased rate or difficulty breathing or some loss of scalp hair, vaginal bleeding or discharge, severe or sudden vision changes, headache, loss of coordination, slurred speech, trouble breathing, weakness or numbness in arms or legs, skin rash or itching.

## **LH-RH ANALOGUES**

### **GOSERELIN**

**MECHANISM OF ACTION:** It binds to LHRH receptors on pituitary gland cells and form clusters, which are then sequestered within the cell, thereby reducing the number of unoccupied LHRH receptors. These unoccupied receptors are maintained at low levels by the presence of the LHRH analogue, ultimately resulting in reduced LH secretion. In turn, the reduced plasma LH causes a decrease in circulatory estradiol (the main source of estrogen in premenopausal women) to levels comparable to the postmenopausal state within 21 days, which are maintained with continued administration of LHRH analogues.

**SIDE EFFECTS:** Rarely, hypersensitivity reactions (including urticaria and anaphylaxis), Changes in blood pressure, manifest as hypotension or hypertension, ovarian cyst formation have been reported.

## **ANTI-ESTROGENS**

### **RALOXIFENE**

**MECHANISM OF ACTION:** The biological actions of raloxifene are largely mediated through binding to estrogen receptors. This binding results in activation of certain estrogenic pathways and blockade of others. Thus, raloxifene is an estrogen agonist/antagonist, commonly referred to as a selective estrogen receptor modulator (SERM).

**SIDE EFFECTS:** Hot flashes, sweating, or leg cramps may occur. Raloxifene may infrequently cause serious blood clots to form in the legs, lungs, or eyes, leg swelling/pain, trouble breathing, chest pain and vision changes

## **TAMOXIFEN**

**MECHANISM OF ACTION:** Tamoxifen citrate is a nonsteroidal agent that has demonstrated potent antiestrogenic properties due to its ability to compete with estrogen for binding sites in target tissues such as breast. Tamoxifen inhibits the induction of rat mammary carcinoma induced by dimethylbenzanthracene (DMBA) and causes the regression of already established DMBA-induced tumors. In this rat model, tamoxifen appears to



exert its antitumor effects by binding the estrogen receptors

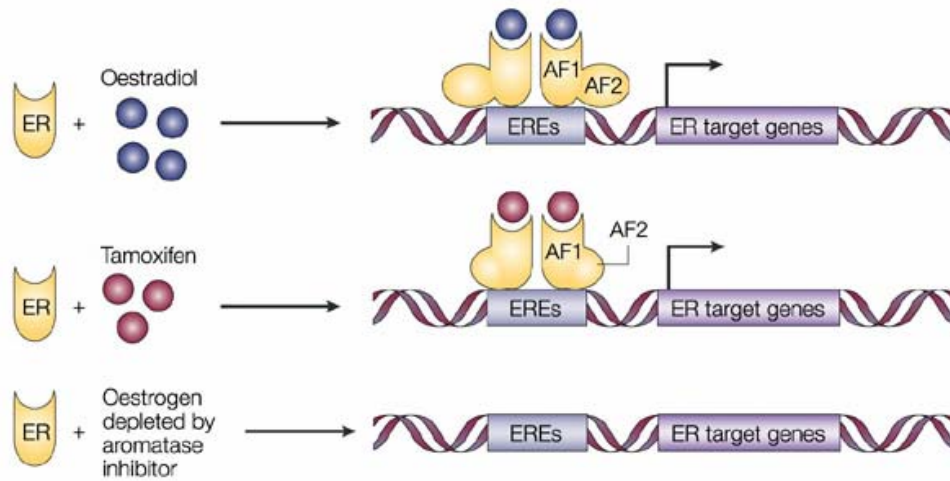
**SIDE EFFECTS:** Hot flashes, irregular mensrual cycles, unusual vaginal discharge or bleeding, irritation of skin around vagina.

## **TOREMIFENE**

**MECHANISM OF ACTION:** Toremifene is a nonsteroidal triphenylethylene derivative. Toremifene binds to estrogen receptors and may exert estrogenic, antiestrogenic, or both activities, depending upon the duration of treatment, animal species, gender, target organ, or endpoint selected. The antitumor effect of toremifene in breast cancer is believed to be mainly due to its antiestrogenic effects, ie, its ability to compete with estrogen for binding sites in the cancer, blocking the growth-stimulating effects of estrogen in the tumor.

**SIDE EFFECTS:** Hot Flashes, Sweating, Nausea, Vaginal Discharge, Dizziness, Edema, Vomiting, Vaginal Bleeding. nausea and vomiting, fatigue, thrombophlebitis,

depression, lethargy, anorexia, ischemic attack, arthritis, pulmonary embolism, and myocardial infarction).



**FIGURE 10**

Both oestradiol and tamoxifen bind to the estrogen receptor (ER) and lead to dimerization, conformational change in the activating function-2 (AF2) domain of ER and binding to estrogen-response elements (EREs). The conformational change with tamoxifen is different from that with oestradiol and leads to persistent but less efficient transcription of most estrogen-dependent genes. Estrogen depletion leads to an absence of estrogen-dependent transcription.

## REVIEW OF LITERATURE

Malita FM *et al.* (2009) made a study to compare the relationship between several insulin sensitivity indices with cardiometabolic risk factors in overweight and obese postmenopausal women. They concluded that the different methods of measuring and/or expressing insulin sensitivity display variations for associations with cardiometabolic risk factors. Therefore interpretations of relationships between insulin sensitivity indices and cardiometabolic risk factors should take into account the method used to estimate and express insulin sensitivity.

Montazeri *et al.* (2008) examined the relationship between anthropometric variables and risk of breast cancer in post-menopausal women. He reported that weight gain might be a better measure of adult obesity than BMI or body fat mass or fat free mass components of BMI are found to be more discriminant factors for breast cancer incidence risk than the commonly used BMI.

Wang *et al.* (2007) demonstrated for the first time that adiponectin could modulate the GSK3 $\beta$ / $\beta$ -catenin pathway in human breast cancer cells, which might play a critical role in mediating the inhibitory effects of adiponectin on mammary tumorigenesis. Further suggested that the cross-talks between adipokines and Wnt signaling pathways might represent a critical mechanism underlying the development of obesity-related cancers.

Lorincz *et al.* (2006) recognized the need to identify and alter the modifiable breast cancer risks mainly focusing on obesity. He summarized that maintenance of a lean body mass offers a way in which women can modestly to significantly reduce their relative breast cancer risk. He concluded that examination of pathways that are altered in obesity may offer new targets for breast cancer therapy.

Kaur *et al.* (2005) suggested that higher BMI is associated with a more advanced stage of breast cancer at diagnosis. Further investigated the relationship between indicators of body size and breast cancer

incidences. Studies on attained height in relation to breast cancer occurrence from diverse populations consistently suggested that taller women are a greater risk for breast cancer regardless of menopausal status.

Wolf *et al.* (2005) reported that incidence of both breast cancer and type 2 diabetes is high in elderly people and both share a common risk factor—obesity. He proposed that three mechanisms contribute to the association between type 2 diabetes and breast cancer: activation of the insulin pathway, activation of the insulin-like-growth-factor pathway, and impaired regulation of endogenous sex hormones.

Calle *et al.* (2004) explained the mechanisms relating adiposity to cancer risk. His study indicated that the relationship between BMI and breast cancer can be explained by the adiposity-related increase in endogenous estrogen levels.

Gupta *et al.* (2004) made a study to evaluate surrogate markers of insulin resistance in forty euglycemic healthy subjects. The surrogate markers were significantly correlated to MCR and found that there was no significant

superiority of one marker over the other. Finally, they suggested that measuring insulin levels alone in a single fasting sample can serve as a simple, cheap and convenient indirect qualitative index of IR.

McTiernan *et al.* (2003) studied the association between BMI, body fat mass and percent body fat with concentration of estrone, estradiol, testosterone, SHBG, DHEA, free estradiol and free testosterone. He reported that obese women ( $\text{BMI} \geq 30$ ) had 35% high concentration of estrone and 130% higher concentration of estradiol compared with lighter-weight women ( $\text{BMI} < 22$ ). He further indicated that overall amount of body fat may be more important than distribution of body fat in determining sex hormone concentrations in post-menopausal women with breast cancer.

Soonthornpun *et al.* (2003) attempted to develop a new equation that is more suitable than others in assessing insulin sensitivity in subjects with normal glucose tolerance. They tested the hypothesis that equation for  $\text{ISI}_{\text{OGTT}}$  derived from the area above the glucose curve correlated with  $\text{ISI}_{\text{Clamp}}$ , and the degree of correlation was stronger than that of other previously reported  $\text{ISI}_{\text{OGTT}}$ .

Takashi Kadowaki *et al.*, 2003 endeavored to depict the molecular mechanism of insulin resistance, focusing on the function of adipocyte. The study provided the first direct evidence that adiponectin plays a protective role against insulin resistance and atherosclerosis in vivo. These observations clearly indicated that adiponectin is indeed an insulin-sensitizing hormone and exerts a protective role against insulin resistance in vivo. It is evident from the preceding results that PPAR<sub>γ</sub> is a key molecule to mediate high-fat-diet induced obesity and that depression of adiponectin action have crucial roles in insulin resistance induced by obesity. He confirmed that replenishment of adiponectin represents a novel treatment strategy for insulin resistance and Type II diabetes.

Radikova *et al.* (2003) evaluated critically the use of some of the proposed indices in insulin sensitivity estimation- indices calculated using fasting plasma concentrations of insulin, glucose and triglycerides and indices calculated by using plasma concentrations of insulin and glucose obtained during 120 min of a standard OGTT.

Stoll *et al.* (2002) showed that long continued insulin resistance was associated with upper abdominal adiposity can lead to aberrant insulin signalling through the insulin receptor 1 pathway in the cell. The evidence pointed to a mechanism by which upper abdominal obesity and associated insulin resistance may increase the risk of breast cancer in women.

Zofia Cervenakova *et al.* (2002) made a study to evaluate the influence of body composition on various indices of insulin sensitivity and secretion in subjects with normal glucose tolerance. The results showed that all subjects had a normal glucose tolerance and no difference was found in course of glycemia, while overweight subjects had an enhanced insulin response. In overweight individuals the insulin sensitivity indices were found to be significantly increased. It was finally concluded that the easiest way to predict insulin resistance in normal glucose tolerance is to calculate an index from glucose and insulin concentration during an OGTT.



Stumvoll *et al.* (2000) evaluated to what extent insulin sensitivity and insulin release are interdependent. He predicted metabolic clearance rate of glucose and insulin sensitivity index for 104 non-diabetic volunteers from their OGTT values. He concluded that it is possible to obtain an individual's insulin sensitivity and  $\beta$ -cell function from BMI and values for plasma glucose and insulin obtained during an OGTT.

## MATERIALS AND METHODS

- Xylene-manufactured by Fischer Chemic Ltd.,
- Sterile Absorbent Cotton-manufactured by The Ramaraju Surgical Cotton Mills Ltd.,
- Sterile blood lancets-manufactured by Medipoint, Inc.,
- Blood glucose test strips- manufactured by Major Biosystem Corp.
- Glucose-D-(1 kg)-manufactured by Avalon Cosm. Pvt. Ltd.,
- Centrifuge- Eppendorf Ltd.,
- Centrifuge tubes (1 ml)- Eppendorf Ltd.,
- Disposable syringe (5 ml)-BD
- Vaccum blood collection tube (5ml)- manufactured by peerless biotech private ltd.,
- Disposable filler-BD
- Precision pipettes and tips, 0.05 ml, 0.1 ml – Tarsons Products Pvt. Ltd.,
- Disposable pipette tips- Himedia
- Distilled water
- Absorbent paper
- Microtiter plate reader- Tarsons Products Pvt. Ltd.,

- Monoclonal anti Insulin antibody coated microtiter plate with 96 wells.
- Enzyme conjugate reagent, 12 ml.
- Insulin reference standards containing; 0, 5, 25, 50, 100, and 200 uIU/ml. lyophilized 0.5mlx2sets.
- Wash Solution Concentrate, 50X, 15ml
- Chemiluminescence Reagent A, 6.0 ml.
- Chemiluminescence Reagent B, 6.0 ml.
- Body measurement table
- Toledo self-zeroing weight scale
- Steel measuring tape
- Small sliding caliper

#### **REAGENTS FOR INSULIN ASSAY:**

1. All reagents were kept at room temperature (18-25°C) and mixed gently by inverting or swirling without formation of foam.
2. 1 volume of Wash Buffer (50x) was diluted with 49 volumes of distilled water
3. Each lyophilized standard was reconstituted with 0.5 ml of distilled water and was allowed to stand for 20 minutes.

**INSTRUMENT:**

|                    |   |  |
|--------------------|---|--|
| OGTT<br>monitoring | - | Gluco Chek blood glucose<br><br>system- manufactured by Major<br>Biosystem Corp Taiwan |
| INSULIN ASSAY      | - | Immulite 2000  |
| Vortex mixer       | - | Remi Motors Ltd.,  |

## METHODOLOGY

### **PRINCIPLE FOR ANTHROPOMETRIC MEASUREMENTS:**

Anthropometry is the study of the measurement of the human body in terms of the dimensions of bone, muscle, and adipose (fat) tissue. Measures of subcutaneous adipose tissue are important because individuals with large values are reported to be at increased risks for hypertension, adult-onset diabetes mellitus, cardiovascular disease, gallstones, arthritis, and other disease, and forms of cancer.

Anthropometric measurements such as skinfolds and circumferences and bioelectrical impedance (a method used to estimate the amount of lean tissue) will allow cross-sectional analysis of the relationship between obesity and risk of disease. Body measurements are always taken on the right side of the body. All measurements, except skinfolds, should be taken to the nearest tenth of a centimeter or 1.0 millimeter. Skinfold measurements are taken to the nearest 0.1 millimeter.

## **1. WEIGHT:**

The electronic digital scale was adjusted to kilogram mode and the digital LED readout showed "0" before weighing a sampled person.

If it does not, adjust on the keyboard scale to zero the scale. The sampled person stood on the center of the weight scale platform and the weight was recorded in kilograms in the automated system.

## **2. STANDING HEIGHT**

The sampled person (SP) stood erect on the floor with her back to the vertical backboard as the weight of the participant should be evenly distributed on both feet. The heels of the feet were placed together with both heels touching the base of the vertical board. The feet should be pointed slightly outward at a 60 degree angle. If the SP has knock knees, the feet should be separated so that the inside of the knees are in contact but not overlapping. The buttocks, scapulae, and head were

positioned in contact with the vertical backboard. The arms were positioned to hang freely by the sides of the trunk with palms facing the thighs.

The SP was asked to inhale deeply and to stand fully erect without altering the position of the heels. The SP's head was maintained in the Frankfort Horizontal Plane position. Hair ornaments, buns, braids, etc. were removed to obtain an accurate measurement.

### **3. FOREARM CIRCUMFERENCE**

The SP stood with the elbow relaxed so that the right arm hangs freely to the side. The measuring tape was placed around the upper arm at the marked point perpendicular to the long axis of the upper arm (from upper arm length). The tape was again held so that the zero end is held below the measurement value. The tape should rest on the skin surface, but not pulled tight enough

to compress the skin. The arm circumference was recorded to the nearest 0.1 cm.

#### **4. ABDOMINAL (WAIST) CIRCUMFERENCE**

The examiner stood behind the SP and palpate the hip area for the right iliac crest and a horizontal line was marked at the high point of the iliac crest and then made to cross the line to indicate the midaxillary line of the body. Then the waist circumference was measured without compressing the skin. The measurement was made at minimal respiration to the nearest 0.1 cm.

#### **5. BUTTOCKS (HIP) CIRCUMFERENCE**

The SP was made to stand erect with feet together and weight evenly distributed on both feet. The measurement was taken by placing the measuring tape around the buttocks. The tape was placed at the maximum extension of the buttocks. The zero end of the tape was held under the measurement value.



## **6. WRIST BREADTH**

The SP was made to extend the right arm keeping the arm straight and near the side of the chest. The most prominent aspect of the ulnar styloid process was palpated with the middle finger of the right hand and the right blade of the caliper was made to slide on to this landmark. The most prominent aspect of the radial styloid process was located with the middle finger of the left hand. Firm pressure was then applied and the breadth was recorded to the nearest 0.1 cm.

### **Methodology for cluster analysis**

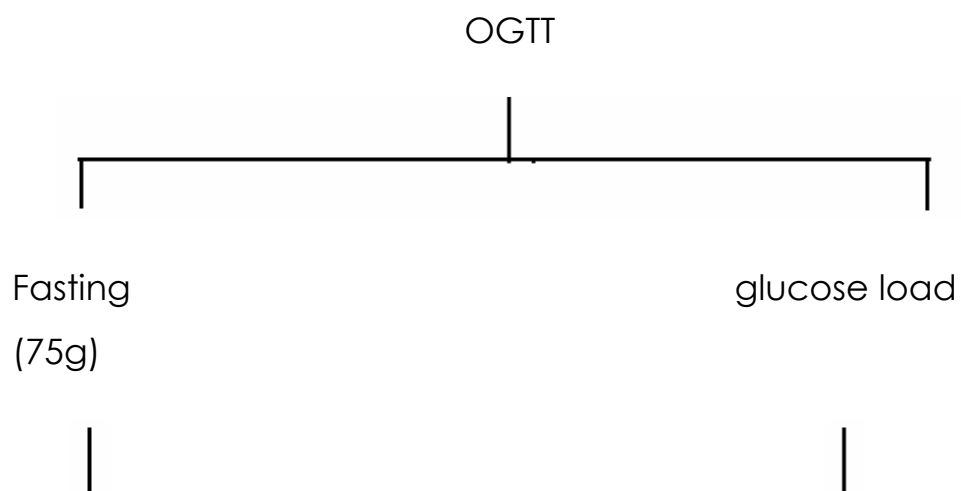
Data obtained often fall naturally into groups / clusters, of observations, where the characteristics of objects in the same cluster are similar. We further stratified the population using a software program and performed clustered analysis.

K-means clustering (partitioning) treats observations in the data as objects having locations and distances

from each other. It partitions the objects into K mutually exclusive clusters, such that objects within each cluster are as close to each other as possible, and as far from objects in other clusters as possible. Each cluster is characterized by its centroid (center point). Of course, the distances used in clustering often do not represent spatial distances. Hierarchical clustering investigates grouping in the data, simultaneously over a variety of scales of distance, by creating a cluster tree. The tree is not a single set of clusters, as in K-Means, but rather a multi-level hierarchy, where clusters at one level are joined as clusters at the next higher level. This allows us to decide what scale or level of clustering is most appropriate in our application.

Variables were analyzed by a computer program which permits direct visualization of the three dimensional shape of the data set and the subjects were classified by means of a computer classification which employed a cluster analysis technique. This resulted in the definition of three groups.

### ORAL GLUCOSE TOLERANCE TEST



(Done at 8.30 a.m after 10-12 hrs  
half-an-hour overnight fasting)  
from fasting)

|

Blood collection by  
collection by  
finger prick method  
method

|

Collection of blood  
sample at 0 min

|

Blood glucose monitoring  
monitoring

(Done after

|

Blood

finger prick

|

Sample collection  
of blood at  
30, 60, 90, 120 min  
respectively

|

Blood glucose

## **PRINCIPLE FOR INSULIN ASSAY**

The Insulin Quantitative Test Kit is based on a solid phase enzyme-linked immunosorbent assay. The assay system utilizes one anti-Insulin antibody for solid phase (microtiter wells) immobilization and another anti-Insulin antibody in the antibody-enzyme (horseradish peroxidase) conjugate solution. The standards and test specimen (serum) are added to the Insulin antibody coated microtiter wells. Then anti- Insulin antibody labeled with horseradish peroxidase (conjugate) is added. If human Insulin is present in the specimen, it will combine with the antibody on the well and the enzyme conjugate resulting in the Insulin molecules being sandwiched between the solid phase and enzyme-linked antibodies. After 1 hour incubation at room temperature, the wells are washed with water to remove unbound labeled antibodies. A solution of chemiluminescent substrate is then added and read relative light units (RLU) in a Lumino meters. The intensity of the emitting light is proportional to the amount of enzyme present and is directly related to the amount of

insulin in the sample. By reference to a series of insulin standards assayed in the same way, the concentration of insulin in the unknown sample is quantified.

#### **I. OGTT:**

Currently two methods are available:

- a. Traditional Method- Finger Prick Method
- b. Glucose Oxidase Method

#### **a. TRADITIONAL METHOD:**

Blood glucose meter is a small portable machine used to monitor blood glucose levels.

#### **PROCEDURE:**

1. Hands were washed in warm, soapy water and dried thoroughly.
2. Finger tip was cleansed using sterile cotton soaked in spirit
3. The finger was then allowed to dry.
4. The test strip was inserted into the slot of the glucose meter with the black bars of the test strip facing up.
5. Fingertip was pricked using a sterile lancet and gently squeezed to get a drop of blood.
6. The blood drop was placed on the test strip, previously inserted into the glucose meter and monitored for blood glucose levels.
7. The glucose meter soon displays the blood glucose level as a number in mg/dl unit.

## **INSULIN ASSAY**

### **PROCEDURE FOR SERUM COLLECTION**

1. A tourniquet was placed around the upper arm to apply pressure and cause the veins to swell with blood.
2. Blood was drawn from a vein in the arm inside of the elbow after cleaning the skin surface with an antiseptic and collected in a syringe.
3. The blood was then collected in a plain red-top venipuncture tube without additives.
4. The blood was then allowed to clot.
5. The specimen was then centrifuged to separate the serum from cells.

## **INSULIN ASSAY PROCEDURE**

1. Desired number of coated wells were secured in the holder. 50 $\mu$ l of Insulin standards, specimens, and controls were added into the appropriate wells and mixed gently for 10 seconds.
2. 100 $\mu$ l of enzyme conjugate reagent was added into each well and mixed gently for 30 seconds to facilitate complete mixing and incubated at room temperature for 60 minutes.
3. The incubation mixture was then removed and the microtiter plate was rinsed 5 times with 1 x wash



buffer (300µl each well). Then the residual water droplets were removed using absorbent paper.

4. 100 µl Chemiluminescence substrate solution was then added into each well and gently mixed for 5 seconds.
5. After 5 minutes, the wells were observed using a chemiluminescence microwell reader.

## METHODOLOGY FOR CALCULATING HOMA-IR

Homeostasis model assessments of insulin resistance (HOMA2-IR) and pancreatic beta-cell function (HOMA2-%B) were completed using the HOMA Calculator version 2.2.2 (<http://www.dtu.ox.ac.uk>, accessed Feb 2010).

## INDICES CALCULATION

The indices evaluated were selected *a priori* based on their performance in previous investigations. The **insulin sensitivity index** (ISI) was calculated from the oral glucose tolerance test according to the formula:  $ISI = 10,000 \div \sqrt{([fasting\ plasma\ glucose \times fasting\ plasma\ insulin] \times [mean\ OGTT\ glucose \times mean\ OGTT\ insulin])}$ .

**Beta-cell function** was assessed as corrected incremental insulin response (CIR) during the glucose-tolerance test according to the formula:

$$\text{CIR} = (100 \times \text{insulin at 30 min}) \div ([\text{glucose at 30 min}] \times [\text{glucose at 30 min} - 3.89])$$
 (or) as a disposition index (i.e., insulin secretion adjusted for insulin sensitivity, or  $\text{CIR} \times \text{ISI}$ ).

## OBJECTIVE

- ❖ To stratify the female population based on their obesity and body fat distributions using cluster analysis without relating to conventional obesity cut-off values.
- ❖ To study insulin response (sensitivity x resistance) using indices of surrogate measures obtained from OGTT data.
- ❖ To identify the hormonal parameters that are significantly altered in obese breast cancer patients and to exploit them as screening markers along with body mass index (BMI) and body fat mass (BFM).
- ❖ To build a comprehensive questionnaire for breast cancer risk prediction using related variables and the symptoms associated with hormonal variations in breast cancer.

## PURPOSE OF STUDY

According to estimates of the International Obesity Task Force, 1,7 billion people are exposed to health risks related to body weight, while the increase in Body Mass Index (BMI) is responsible for more than 2.5 million deaths annually, which is expected to double by 2030. The aim is to define obesity using anthropometric measures particularly in obese post-menopausal women.

Assessment of insulin resistance is of great importance in the study of epidemiology and pathophysiology of major public health problems and in following the clinical course of patients on various therapeutic regimens. It is also of our interest to evaluate the insulin resistance in obese post-menopausal women who are at high risk for breast cancer using a simple oral glucose tolerance test (OGTT).

Studying about relevant risk factors of breast cancer and their prevalence is essential in the breast cancer risk prediction among individuals of high risk group.

## RESULTS AND DISCUSSION

We measured the anthropometric measurements for 70 female individuals and obtained the measurements of height, weight, circumferences of wrist, forearm, waist and hip.

**TABLE 1**

| <b>CODE</b> | <b>AGE</b> | <b>HT<br/>(m)</b> | <b>TBW<br/>(kg)</b> | <b>WRIST<br/>(cm)</b> | <b>FOREARM<br/>(cm)</b> | <b>WAIST<br/>(cm)</b> | <b>HIP<br/>(cm)</b> |
|-------------|------------|-------------------|---------------------|-----------------------|-------------------------|-----------------------|---------------------|
| 1           | 35         | 1.52              | 40                  | 5.9                   | 8.5                     | 26.5                  | 33.8                |
| 2           | 25         | 1.472             | 42                  | 5.5                   | 8.4                     | 31.8                  | 33.5                |
| 3           | 24         | 1.575             | 55                  | 6                     | 9                       | 31                    | 38.3                |
| 4           | 24         | 1.665             | 61                  | 6                     | 8.9                     | 35.2                  | 41                  |
| 5           | 24         | 1.528             | 46.5                | 6.1                   | 9.1                     | 29                    | 35.1                |
| 6           | 30         | 1.55              | 63.5                | 6.5                   | 9.8                     | 35                    | 41.6                |
| 7           | 38         | 1.58              | 68.5                | 6.9                   | 10.2                    | 37                    | 41.8                |
| 8           | 24         | 1.55              | 43                  | 5.4                   | 7.9                     | 27                    | 35.1                |
| 9           | 25         | 1.6               | 66                  | 6.1                   | 9.6                     | 40.8                  | 42.3                |
| 10          | 21         | 1.57              | 43                  | 5.5                   | 8.4                     | 26.5                  | 33.5                |
| 11          | 24         | 1.64              | 49                  | 5.6                   | 8.2                     | 27                    | 34.9                |
| 12          | 24         | 1.66              | 55                  | 5.9                   | 9                       | 30                    | 39.3                |
| 13          | 25         | 1.58              | 43                  | 5.4                   | 8                       | 28                    | 35                  |

## Results and Discussion

|    |    |       |      |     |      |      |      |
|----|----|-------|------|-----|------|------|------|
| 14 | 28 | 1.61  | 50   | 5.6 | 8.8  | 30   | 38.5 |
| 15 | 23 | 1.45  | 42   | 5.4 | 8.4  | 26   | 32.9 |
| 16 | 23 | 1.67  | 54   | 5.2 | 8.1  | 29.5 | 37.9 |
| 17 | 30 | 1.57  | 76   | 6.3 | 10.9 | 44   | 45.5 |
| 18 | 23 | 1.656 | 41   | 5.3 | 7.8  | 29   | 34.5 |
| 19 | 30 | 1.615 | 56   | 6.4 | 9.6  | 35.3 | 42   |
| 20 | 22 | 1.615 | 50   | 6.1 | 8.5  | 32.8 | 36.2 |
| 21 | 47 | 1.478 | 76   | 7   | 11.4 | 45   | 48.5 |
| 22 | 39 | 1.56  | 40   | 5.8 | 8.5  | 31.6 | 33   |
| 23 | 21 | 1.5   | 65   | 6.4 | 10   | 39.8 | 43.5 |
| 24 | 20 | 1.59  | 35   | 5.1 | 7.6  | 27.2 | 32.1 |
| 25 | 21 | 1.568 | 50   | 5.8 | 8.9  | 32.8 | 35.5 |
| 26 | 21 | 1.564 | 39   | 5.6 | 8.3  | 29.2 | 33.8 |
| 27 | 20 | 1.502 | 42   | 6.4 | 8.9  | 30.6 | 34.1 |
| 28 | 25 | 1.543 | 52   | 5.9 | 9    | 32   | 39.3 |
| 29 | 23 | 1.668 | 40   | 7.8 | 7.9  | 30.2 | 33.2 |
| 30 | 28 | 1.472 | 41   | 6   | 8.9  | 31.8 | 34   |
| 31 | 22 | 1.57  | 46   | 5.8 | 8.4  | 35.3 | 36   |
| 32 | 20 | 1.536 | 47   | 6   | 9    | 32.5 | 36.8 |
| 33 | 19 | 1.578 | 43   | 6.1 | 8.6  | 30.1 | 33   |
| 34 | 18 | 1.617 | 47   | 6.1 | 9    | 31.5 | 33.8 |
| 35 | 21 | 1.525 | 45.5 | 5.8 | 8.9  | 31.9 | 34.8 |

|    |    |       |      |     |      |      |      |
|----|----|-------|------|-----|------|------|------|
| 36 | 26 | 1.57  | 49   | 5.8 | 8.5  | 32   | 36   |
| 37 | 20 | 1.563 | 42.5 | 6   | 8.5  | 30.7 | 33   |
| 38 | 21 | 1.612 | 51   | 6.2 | 8.8  | 34.3 | 35.5 |
| 39 | 29 | 1.59  | 56.5 | 6   | 10.1 | 35.8 | 38.8 |
| 40 | 42 | 1.582 | 47   | 5.6 | 8.8  | 34   | 35.3 |
| 41 | 26 | 1.54  | 75   | 7.5 | 10.6 | 42.8 | 42   |
| 42 | 25 | 1.42  | 44   | 5.7 | 8.5  | 34.5 | 36   |
| 43 | 28 | 1.603 | 40   | 5.2 | 7.9  | 32   | 34.3 |
| 44 | 50 | 1.48  | 50   | 6.2 | 8.9  | 37.8 | 39.8 |
| 45 | 65 | 1.457 | 45   | 6.3 | 9    | 36.9 | 35.5 |
| 46 | 40 | 1.478 | 45.5 | 6.2 | 8.8  | 33   | 36   |
| 47 | 37 | 1.507 | 45.5 | 6.8 | 9.3  | 35   | 34.2 |
| 48 | 27 | 1.538 | 54.5 | 6.6 | 9.1  | 39   | 38.8 |
| 49 | 35 | 1.485 | 52   | 6.1 | 9.3  | 34.2 | 39.9 |
| 50 | 52 | 1.55  | 52.5 | 6.1 | 8.8  | 38.3 | 40.8 |
| 51 | 55 | 1.582 | 64   | 6.2 | 9.8  | 38.3 | 42.8 |
| 52 | 60 | 1.42  | 47   | 6.4 | 9    | 35.8 | 36.8 |
| 53 | 33 | 1.57  | 58   | 6.5 | 9.5  | 40   | 38   |
| 54 | 41 | 1.46  | 48   | 6.1 | 9.2  | 36.9 | 35   |
| 55 | 30 | 1.346 | 35   | 6   | 9    | 27.6 | 33   |
| 56 | 49 | 1.53  | 55.5 | 6.8 | 9    | 38.7 | 40.1 |
| 57 | 54 | 1.6   | 59   | 6.6 | 9.8  | 36   | 43   |

## Results and Discussion

|    |    |       |      |     |      |      |      |
|----|----|-------|------|-----|------|------|------|
| 58 | 48 | 1.58  | 49   | 5.7 | 8.8  | 34.3 | 35.8 |
| 59 | 52 | 1.45  | 49   | 6.6 | 9.1  | 36.1 | 37.1 |
| 60 | 60 | 1.54  | 58   | 6.8 | 9.3  | 41   | 40.3 |
| 61 | 49 | 1.42  | 64   | 6.6 | 9.6  | 42.5 | 45.2 |
| 62 | 55 | 1.51  | 63.1 | 6.4 | 9.7  | 38.1 | 42.1 |
| 63 | 53 | 1.53  | 61.4 | 6.3 | 9.7  | 39.9 | 43.2 |
| 64 | 49 | 1.59  | 52.3 | 5.7 | 8.9  | 28.1 | 39.2 |
| 65 | 50 | 1.592 | 69   | 6.9 | 10.3 | 38   | 41   |
| 66 | 46 | 1.55  | 73.2 | 7.1 | 10.9 | 43.2 | 47.1 |
| 67 | 51 | 1.521 | 48.4 | 5.9 | 8.7  | 33.4 | 36.2 |
| 68 | 53 | 1.692 | 69   | 7.3 | 9.8  | 38.2 | 43.4 |
| 69 | 47 | 1.581 | 51   | 5.8 | 9.1  | 29.1 | 35.7 |
| 70 | 58 | 1.542 | 63   | 6.1 | 9.7  | 36.4 | 39.9 |



We calculated body mass index (BMI) and body fat mass (BFM) using the data obtained from anthropometric measurements and the values are tabulated.

$$\text{BMI} = \frac{\text{Body Weight (Kg)}}{\text{Height}^2 (\text{m}^2)}$$

$$\text{BFM} = \frac{\text{BFW} \times 100}{\text{TBW}}$$

$$\text{BFM} = \frac{\text{BFW} \times 100}{\text{TBW}}$$

$$\text{BFM} = \frac{\text{BFW} \times 100}{\text{TBW}}$$

Body fat weight (BFW) = Body fat Weight (TBW) – Lean Body Mass (LBM)

LBM = Factor 1 + ((factor 2 +factor 5) – (factor 3 +factor 4))

Factor 1 = TBW x 0.732) + 8.987

Factor 2 =  $\frac{\text{Wrist circumference}}{3.140}$

3.140

Factor 3 = Waist circumference x 0.157

Factor 4 = Hip circumference x 0.249

Factor 5 = Forearm circumference x 0.434

## CONVERSION FACTORS

Height (m) → x 39.37 → Height (inch)

Weight (kg) → x 2.2046 → Weight (lb)

**CALCULATION OF OBESITY MARKERS (BMI AND BFM)****TABLE 2**

| <b>CODE</b> | <b>AGE</b> | <b>HT<br/>(m)</b> | <b>Ht (inch)<br/>(x 39.37)</b> | <b>TBW<br/>(kg)</b> | <b>Wt (lb)<br/>(x2.2046)</b> | <b>WRIST</b> | <b>FORE-<br/>ARM</b> | <b>WAIST</b> | <b>HIP</b> | <b>TBW<br/>(lb)</b> |
|-------------|------------|-------------------|--------------------------------|---------------------|------------------------------|--------------|----------------------|--------------|------------|---------------------|
| 1           | 35         | 1.52              | 59.8424                        | 40                  | 88.184                       | 5.9          | 8.5                  | 26.5         | 33.8       | 64.55069            |
| 2           | 25         | 1.472             | 57.95264                       | 42                  | 92.5932                      | 5.5          | 8.4                  | 31.8         | 33.5       | 67.77822            |
| 3           | 24         | 1.575             | 62.00775                       | 55                  | 121.253                      | 6            | 9                    | 31           | 38.3       | 88.7572             |
| 4           | 24         | 1.665             | 65.55105                       | 61                  | 134.4806                     | 6            | 8.9                  | 35.2         | 41         | 98.4398             |
| 5           | 24         | 1.528             | 60.15736                       | 46.5                | 102.5139                     | 6.1          | 9.1                  | 29           | 35.1       | 75.04017            |
| 6           | 30         | 1.55              | 61.0235                        | 63.5                | 139.9921                     | 6.5          | 9.8                  | 35           | 41.6       | 102.4742            |
| 7           | 38         | 1.58              | 62.2046                        | 68.5                | 151.0151                     | 6.9          | 10.2                 | 37           | 41.8       | 110.5431            |
| 8           | 24         | 1.55              | 61.0235                        | 43                  | 94.7978                      | 5.4          | 7.9                  | 27           | 35.1       | 69.39199            |

A Study on Insulin Resistance and Obesity among Women at High Risk for Breast Cancer  
Using Cluster Analysis

# Results and Discussion

|    |    |       |          |    |          |     |      |      |      |          |
|----|----|-------|----------|----|----------|-----|------|------|------|----------|
| 9  | 25 | 1.6   | 62.992   | 66 | 145.5036 | 6.1 | 9.6  | 40.8 | 42.3 | 106.5086 |
| 10 | 21 | 1.57  | 61.8109  | 43 | 94.7978  | 5.5 | 8.4  | 26.5 | 33.5 | 69.39199 |
| 11 | 24 | 1.64  | 64.5668  | 49 | 108.0254 | 5.6 | 8.2  | 27   | 34.9 | 79.07459 |
| 12 | 24 | 1.66  | 65.3542  | 55 | 121.253  | 5.9 | 9    | 30   | 39.3 | 88.7572  |
| 13 | 25 | 1.58  | 62.2046  | 43 | 94.7978  | 5.4 | 8    | 28   | 35   | 69.39199 |
| 14 | 28 | 1.61  | 63.3857  | 50 | 110.23   | 5.6 | 8.8  | 30   | 38.5 | 80.68836 |
| 15 | 23 | 1.45  | 57.0865  | 42 | 92.5932  | 5.4 | 8.4  | 26   | 32.9 | 67.77822 |
| 16 | 23 | 1.67  | 65.7479  | 54 | 119.0484 | 5.2 | 8.1  | 29.5 | 37.9 | 87.14343 |
| 17 | 30 | 1.57  | 61.8109  | 76 | 167.5496 | 6.3 | 10.9 | 44   | 45.5 | 122.6463 |
| 18 | 23 | 1.656 | 65.19672 | 41 | 90.3886  | 5.3 | 7.8  | 29   | 34.5 | 66.16446 |
| 19 | 30 | 1.615 | 63.58255 | 56 | 123.4576 | 6.4 | 9.6  | 35.3 | 42   | 90.37096 |
| 20 | 22 | 1.615 | 63.58255 | 50 | 110.23   | 6.1 | 8.5  | 32.8 | 36.2 | 80.68836 |
| 21 | 47 | 1.478 | 58.18886 | 76 | 167.5496 | 7   | 11.4 | 45   | 48.5 | 122.6463 |

A Study on Insulin Resistance and Obesity among Women at High Risk for Breast Cancer  
Using Cluster Analysis

# Results and Discussion

|     |    |       |          |    |          |     |     |      |      |          |
|-----|----|-------|----------|----|----------|-----|-----|------|------|----------|
| 22  | 39 | 1.56  | 61.4172  | 40 | 88.184   | 5.8 | 8.5 | 31.6 | 33   | 64.55069 |
| `23 | 21 | 1.5   | 59.055   | 65 | 143.299  | 6.4 | 10  | 39.8 | 43.5 | 104.8949 |
| 24  | 20 | 1.59  | 62.5983  | 35 | 77.161   | 5.1 | 7.6 | 27.2 | 32.1 | 56.48185 |
| 25  | 21 | 1.568 | 61.73216 | 50 | 110.23   | 5.8 | 8.9 | 32.8 | 35.5 | 80.68836 |
| 26  | 21 | 1.564 | 61.57468 | 39 | 85.9794  | 5.6 | 8.3 | 29.2 | 33.8 | 62.93692 |
| 27  | 20 | 1.502 | 59.13374 | 42 | 92.5932  | 6.4 | 8.9 | 30.6 | 34.1 | 67.77822 |
| 28  | 25 | 1.543 | 60.74791 | 52 | 114.6392 | 5.9 | 9   | 32   | 39.3 | 83.91589 |
| 29  | 23 | 1.668 | 65.66916 | 40 | 88.184   | 7.8 | 7.9 | 30.2 | 33.2 | 64.55069 |
| 30  | 28 | 1.472 | 57.95264 | 41 | 90.3886  | 6   | 8.9 | 31.8 | 34   | 66.16446 |
| 31  | 22 | 1.57  | 61.8109  | 46 | 101.4116 | 5.8 | 8.4 | 35.3 | 36   | 74.23329 |
| 32  | 20 | 1.536 | 60.47232 | 47 | 103.6162 | 6   | 9   | 32.5 | 36.8 | 75.84706 |
| 33  | 19 | 1.578 | 62.12586 | 43 | 94.7978  | 6.1 | 8.6 | 30.1 | 33   | 69.39199 |
| 34  | 18 | 1.617 | 63.66129 | 47 | 103.6162 | 6.1 | 9   | 31.5 | 33.8 | 75.84706 |

A Study on Insulin Resistance and Obesity among Women at High Risk for Breast Cancer  
Using Cluster Analysis

## Results and Discussion

|    |    |       |          |      |          |     |      |      |      |          |
|----|----|-------|----------|------|----------|-----|------|------|------|----------|
| 35 | 21 | 1.525 | 60.03925 | 45.5 | 100.3093 | 5.8 | 8.9  | 31.9 | 34.8 | 73.42641 |
| 36 | 26 | 1.57  | 61.8109  | 49   | 108.0254 | 5.8 | 8.5  | 32   | 36   | 79.07459 |
| 37 | 20 | 1.563 | 61.53531 | 42.5 | 93.6955  | 6   | 8.5  | 30.7 | 33   | 68.58511 |
| 38 | 21 | 1.612 | 63.46444 | 51   | 112.4346 | 6.2 | 8.8  | 34.3 | 35.5 | 82.30213 |
| 39 | 29 | 1.59  | 62.5983  | 56.5 | 124.5599 | 6   | 10.1 | 35.8 | 38.8 | 91.17785 |
| 40 | 42 | 1.582 | 62.28334 | 47   | 103.6162 | 5.6 | 8.8  | 34   | 35.3 | 75.84706 |
| 41 | 26 | 1.54  | 60.6298  | 75   | 165.345  | 7.5 | 10.6 | 42.8 | 42   | 121.0325 |
| 42 | 25 | 1.42  | 55.9054  | 44   | 97.0024  | 5.7 | 8.5  | 34.5 | 36   | 71.00576 |
| 43 | 28 | 1.603 | 63.11011 | 40   | 88.184   | 5.2 | 7.9  | 32   | 34.3 | 64.55069 |
| 44 | 50 | 1.48  | 58.2676  | 50   | 110.23   | 6.2 | 8.9  | 37.8 | 39.8 | 80.68836 |
| 45 | 65 | 1.457 | 57.36209 | 45   | 99.207   | 6.3 | 9    | 36.9 | 35.5 | 72.61952 |
| 46 | 40 | 1.478 | 58.18886 | 45.5 | 100.3093 | 6.2 | 8.8  | 33   | 36   | 73.42641 |
| 47 | 37 | 1.507 | 59.33059 | 45.5 | 100.3093 | 6.8 | 9.3  | 35   | 34.2 | 73.42641 |

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|    |    |       |          |      |          |     |     |      |      |          |
|----|----|-------|----------|------|----------|-----|-----|------|------|----------|
| 48 | 27 | 1.538 | 60.55106 | 54.5 | 120.1507 | 6.6 | 9.1 | 39   | 38.8 | 87.95031 |
| 49 | 35 | 1.485 | 58.46445 | 52   | 114.6392 | 6.1 | 9.3 | 34.2 | 39.9 | 83.91589 |
| 50 | 52 | 1.55  | 61.0235  | 52.5 | 115.7415 | 6.1 | 8.8 | 38.3 | 40.8 | 84.72278 |
| 51 | 55 | 1.582 | 62.28334 | 64   | 141.0944 | 6.2 | 9.8 | 38.3 | 42.8 | 103.2811 |
| 52 | 60 | 1.42  | 55.9054  | 47   | 103.6162 | 6.4 | 9   | 35.8 | 36.8 | 75.84706 |
| 53 | 33 | 1.57  | 61.8109  | 58   | 127.8668 | 6.5 | 9.5 | 40   | 38   | 93.5985  |
| 54 | 41 | 1.46  | 57.4802  | 48   | 105.8208 | 6.1 | 9.2 | 36.9 | 35   | 77.46083 |
| 55 | 30 | 1.346 | 52.99202 | 35   | 77.161   | 6   | 9   | 27.6 | 33   | 56.48185 |
| 56 | 49 | 1.53  | 60.2361  | 55.5 | 122.3553 | 6.8 | 9   | 38.7 | 40.1 | 89.56408 |
| 57 | 54 | 1.6   | 62.992   | 59   | 130.0714 | 6.6 | 9.8 | 36   | 43   | 95.21226 |
| 58 | 48 | 1.58  | 62.2046  | 49   | 108.0254 | 5.7 | 8.8 | 34.3 | 35.8 | 79.07459 |
| 59 | 52 | 1.45  | 57.0865  | 49   | 108.0254 | 6.6 | 9.1 | 36.1 | 37.1 | 79.07459 |
| 60 | 60 | 1.54  | 60.6298  | 58   | 127.8668 | 6.8 | 9.3 | 41   | 40.3 | 93.5985  |

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|    |    |       |          |      |          |     |      |      |      |          |
|----|----|-------|----------|------|----------|-----|------|------|------|----------|
| 61 | 49 | 1.42  | 55.9054  | 64   | 141.0944 | 6.6 | 9.6  | 42.5 | 45.2 | 103.2811 |
| 62 | 55 | 1.51  | 59.4487  | 63.1 | 139.1103 | 6.4 | 9.7  | 38.1 | 42.1 | 101.8287 |
| 63 | 53 | 1.53  | 60.2361  | 61.4 | 135.3624 | 6.3 | 9.7  | 39.9 | 43.2 | 99.08531 |
| 64 | 49 | 1.59  | 62.5983  | 52.3 | 115.3006 | 5.7 | 8.9  | 28.1 | 39.2 | 84.40002 |
| 65 | 50 | 1.592 | 62.67704 | 69   | 152.1174 | 6.9 | 10.3 | 38   | 41   | 111.3499 |
| 66 | 46 | 1.55  | 61.0235  | 73.2 | 161.3767 | 7.1 | 10.9 | 43.2 | 47.1 | 118.1278 |
| 67 | 51 | 1.521 | 59.88177 | 48.4 | 106.7026 | 5.9 | 8.7  | 33.4 | 36.2 | 78.10633 |
| 68 | 53 | 1.692 | 66.61404 | 69   | 152.1174 | 7.3 | 9.8  | 38.2 | 43.4 | 111.3499 |
| 69 | 47 | 1.581 | 62.24397 | 51   | 112.4346 | 5.8 | 9.1  | 29.1 | 35.7 | 82.30213 |
| 70 | 58 | 1.542 | 60.70854 | 63   | 138.8898 | 6.1 | 9.7  | 36.4 | 39.9 | 101.6673 |



## Results and Discussion

| CODE | FACTOR 1 | FACTOR 2 | FACTOR 3 | FACTOR 4 | FACTOR 5 | LBM      | BFW      | BFM      | BMI (m)  | BMI(lb)  |
|------|----------|----------|----------|----------|----------|----------|----------|----------|----------|----------|
| 1    | 73.53769 | 1.878981 | 4.1605   | 8.4162   | 3.689    | 66.52897 | 21.65503 | 24.55664 | 17.31302 | 17.3112  |
| 2    | 76.76522 | 1.751592 | 4.9926   | 8.3415   | 3.6456   | 68.82831 | 23.76489 | 25.66591 | 19.38357 | 19.38153 |
| 3    | 97.7442  | 1.910828 | 4.867    | 9.5367   | 3.906    | 89.15732 | 32.09568 | 26.47001 | 22.17183 | 22.1695  |
| 4    | 107.4268 | 1.910828 | 5.5264   | 10.209   | 3.8626   | 97.46483 | 37.01577 | 27.52499 | 22.00399 | 22.00167 |
| 5    | 84.02717 | 1.942675 | 4.553    | 8.7399   | 3.9494   | 76.62635 | 25.88755 | 25.25272 | 19.91619 | 19.91409 |
| 6    | 111.4612 | 2.070064 | 5.495    | 10.3584  | 4.2532   | 101.9311 | 38.06102 | 27.18798 | 26.4308  | 26.42802 |
| 7    | 119.5301 | 2.197452 | 5.809    | 10.4082  | 4.4268   | 109.9371 | 41.07799 | 27.20125 | 27.43951 | 27.43663 |
| 8    | 78.37899 | 1.719745 | 4.239    | 8.7399   | 3.4286   | 70.54843 | 24.24937 | 25.58009 | 17.89802 | 17.89614 |
| 9    | 115.4956 | 1.942675 | 6.4056   | 10.5327  | 4.1664   | 104.6664 | 40.83719 | 28.0661  | 25.78125 | 25.77854 |
| 10   | 78.37899 | 1.751592 | 4.1605   | 8.3415   | 3.6456   | 71.27418 | 23.52362 | 24.81452 | 17.44493 | 17.44309 |
| 11   | 88.06159 | 1.783439 | 4.239    | 8.6901   | 3.5588   | 80.47473 | 27.55067 | 25.50388 | 18.21832 | 18.21641 |
| 12   | 97.7442  | 1.878981 | 4.71     | 9.7857   | 3.906    | 89.03348 | 32.21952 | 26.57215 | 19.95936 | 19.95726 |

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# Results and Discussion

|    |          |          |        |         |        |          |          |          |          |          |
|----|----------|----------|--------|---------|--------|----------|----------|----------|----------|----------|
| 13 | 78.37899 | 1.719745 | 4.396  | 8.715   | 3.472  | 70.45973 | 24.33807 | 25.67366 | 17.2248  | 17.22299 |
| 14 | 89.67536 | 1.783439 | 4.71   | 9.5865  | 3.8192 | 80.9815  | 29.2485  | 26.53407 | 19.28938 | 19.28735 |
| 15 | 76.76522 | 1.719745 | 4.082  | 8.1921  | 3.6456 | 69.85647 | 22.73673 | 24.55551 | 19.97622 | 19.97412 |
| 16 | 96.13043 | 1.656051 | 4.6315 | 9.4371  | 3.5154 | 87.23328 | 31.81512 | 26.72453 | 19.36247 | 19.36044 |
| 17 | 131.6333 | 2.006369 | 6.908  | 11.3295 | 4.7306 | 120.1328 | 47.41682 | 28.30017 | 30.83289 | 30.82965 |
| 18 | 75.15146 | 1.687898 | 4.553  | 8.5905  | 3.3852 | 67.08105 | 23.30755 | 25.78594 | 14.95076 | 14.94918 |
| 19 | 99.35796 | 2.038217 | 5.5421 | 10.458  | 4.1664 | 89.56248 | 33.89512 | 27.45487 | 21.47054 | 21.46828 |
| 20 | 89.67536 | 1.942675 | 5.1496 | 9.0138  | 3.689  | 81.14364 | 29.08636 | 26.38698 | 19.17013 | 19.16811 |
| 21 | 131.6333 | 2.229299 | 7.065  | 12.0765 | 4.9476 | 119.6687 | 47.88089 | 28.57715 | 34.79082 | 34.78716 |
| 22 | 73.53769 | 1.847134 | 4.9612 | 8.217   | 3.689  | 65.89562 | 22.28838 | 25.27486 | 16.43655 | 16.43483 |
| 23 | 113.8819 | 2.038217 | 6.2486 | 10.8315 | 4.34   | 103.18   | 40.11902 | 27.99672 | 28.88889 | 28.88585 |
| 24 | 65.46885 | 1.624204 | 4.2704 | 7.9929  | 3.2984 | 58.12816 | 19.03284 | 24.6664  | 13.84439 | 13.84293 |
| 25 | 89.67536 | 1.847134 | 5.1496 | 8.8395  | 3.8626 | 81.39599 | 28.83401 | 26.15804 | 20.33658 | 20.33444 |
| 26 | 71.92392 | 1.783439 | 4.5844 | 8.4162  | 3.6022 | 64.30896 | 21.67044 | 25.20422 | 15.94377 | 15.9421  |

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## Results and Discussion

|    |          |          |        |        |        |          |          |          |          |          |
|----|----------|----------|--------|--------|--------|----------|----------|----------|----------|----------|
| 27 | 76.76522 | 2.038217 | 4.8042 | 8.4909 | 3.8626 | 69.37094 | 23.22226 | 25.07988 | 18.61699 | 18.61503 |
| 28 | 92.90289 | 1.878981 | 5.024  | 9.7857 | 3.906  | 83.87818 | 30.76102 | 26.8329  | 21.84095 | 21.83865 |
| 29 | 73.53769 | 2.484076 | 4.7414 | 8.2668 | 3.4286 | 66.44216 | 21.74184 | 24.65508 | 14.37699 | 14.37547 |
| 30 | 75.15146 | 1.910828 | 4.9926 | 8.466  | 3.8626 | 67.46628 | 22.92232 | 25.35974 | 18.92205 | 18.92006 |
| 31 | 83.22029 | 1.847134 | 5.5421 | 8.964  | 3.6456 | 74.20692 | 27.20468 | 26.826   | 18.66201 | 18.66005 |
| 32 | 84.83406 | 1.910828 | 5.1025 | 9.1632 | 3.906  | 76.38519 | 27.23101 | 26.28065 | 19.9212  | 19.9191  |
| 33 | 78.37899 | 1.942675 | 4.7257 | 8.217  | 3.7324 | 71.11136 | 23.68644 | 24.98627 | 17.26849 | 17.26668 |
| 34 | 84.83406 | 1.942675 | 4.9455 | 8.4162 | 3.906  | 77.32103 | 26.29517 | 25.37747 | 17.97537 | 17.97348 |
| 35 | 82.41341 | 1.847134 | 5.0083 | 8.6652 | 3.8626 | 74.44964 | 25.85966 | 25.77992 | 19.56463 | 19.56257 |
| 36 | 88.06159 | 1.847134 | 5.024  | 8.964  | 3.689  | 79.60973 | 28.41567 | 26.30462 | 19.8791  | 19.87701 |
| 37 | 77.57211 | 1.910828 | 4.8199 | 8.217  | 3.689  | 70.13503 | 23.56047 | 25.14578 | 17.39686 | 17.39503 |
| 38 | 91.28913 | 1.974522 | 5.3851 | 8.8395 | 3.8192 | 82.85825 | 29.57635 | 26.30538 | 19.62638 | 19.62431 |
| 39 | 100.1648 | 1.910828 | 5.6206 | 9.6612 | 4.3834 | 91.17727 | 33.38263 | 26.80046 | 22.3488  | 22.34645 |
| 40 | 84.83406 | 1.783439 | 5.338  | 8.7897 | 3.8192 | 76.309   | 27.3072  | 26.35418 | 18.77954 | 18.77756 |

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# Results and Discussion

|    |          |          |        |         |        |          |          |          |          |          |
|----|----------|----------|--------|---------|--------|----------|----------|----------|----------|----------|
| 41 | 130.0195 | 2.388535 | 6.7196 | 10.458  | 4.6004 | 119.8309 | 45.51412 | 27.52676 | 31.62422 | 31.62089 |
| 42 | 79.99276 | 1.815287 | 5.4165 | 8.964   | 3.689  | 71.11654 | 25.88586 | 26.68579 | 21.82107 | 21.81877 |
| 43 | 73.53769 | 1.656051 | 5.024  | 8.5407  | 3.4286 | 65.05764 | 23.12636 | 26.22512 | 15.56657 | 15.56493 |
| 44 | 89.67536 | 1.974522 | 5.9346 | 9.9102  | 3.8626 | 79.66768 | 30.56232 | 27.72595 | 22.82688 | 22.82448 |
| 45 | 81.60652 | 2.006369 | 5.7933 | 8.8395  | 3.906  | 72.88609 | 26.32091 | 26.5313  | 21.19793 | 21.1957  |
| 46 | 82.41341 | 1.974522 | 5.181  | 8.964   | 3.8192 | 74.06213 | 26.24717 | 26.16624 | 20.82872 | 20.82653 |
| 47 | 82.41341 | 2.165605 | 5.495  | 8.5158  | 4.0362 | 74.60441 | 25.70489 | 25.62563 | 20.03479 | 20.03269 |
| 48 | 96.93731 | 2.101911 | 6.123  | 9.6612  | 3.9494 | 87.20442 | 32.94628 | 27.42079 | 23.04007 | 23.03765 |
| 49 | 92.90289 | 1.942675 | 5.3694 | 9.9351  | 4.0362 | 83.57727 | 31.06193 | 27.09538 | 23.58036 | 23.57788 |
| 50 | 93.70978 | 1.942675 | 6.0131 | 10.1592 | 3.8192 | 83.29935 | 32.44215 | 28.02983 | 21.85224 | 21.84994 |
| 51 | 112.2681 | 1.974522 | 6.0131 | 10.6572 | 4.2532 | 101.8255 | 39.26888 | 27.83163 | 25.57214 | 25.56945 |
| 52 | 84.83406 | 2.038217 | 5.6206 | 9.1632  | 3.906  | 75.99447 | 27.62173 | 26.65773 | 23.30887 | 23.30641 |
| 53 | 102.5855 | 2.070064 | 6.28   | 9.462   | 4.123  | 93.03656 | 34.83024 | 27.23947 | 23.53037 | 23.52789 |
| 54 | 86.44783 | 1.942675 | 5.7933 | 8.715   | 3.9928 | 77.875   | 27.9458  | 26.40861 | 22.5183  | 22.51593 |

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# Results and Discussion

|    |          |          |        |         |        |          |          |          |          |          |
|----|----------|----------|--------|---------|--------|----------|----------|----------|----------|----------|
| 55 | 65.46885 | 1.910828 | 4.3332 | 8.217   | 3.906  | 58.73548 | 18.42552 | 23.87932 | 19.3187  | 19.31667 |
| 56 | 98.55108 | 2.165605 | 6.0759 | 9.9849  | 3.906  | 88.56188 | 33.79342 | 27.61909 | 23.70883 | 23.70634 |
| 57 | 104.1993 | 2.101911 | 5.652  | 10.707  | 4.2532 | 94.19538 | 35.87602 | 27.58179 | 23.04688 | 23.04445 |
| 58 | 88.06159 | 1.815287 | 5.3851 | 8.9142  | 3.8192 | 79.39678 | 28.62862 | 26.50175 | 19.62826 | 19.6262  |
| 59 | 88.06159 | 2.101911 | 5.6677 | 9.2379  | 3.9494 | 79.2073  | 28.8181  | 26.67715 | 23.30559 | 23.30314 |
| 60 | 102.5855 | 2.165605 | 6.437  | 10.0347 | 4.0362 | 92.3156  | 35.5512  | 27.80331 | 24.45606 | 24.45349 |
| 61 | 112.2681 | 2.101911 | 6.6725 | 11.2548 | 4.1664 | 100.6091 | 40.48529 | 28.69376 | 31.73973 | 31.73639 |
| 62 | 110.8157 | 2.038217 | 5.9817 | 10.4829 | 4.2098 | 100.5991 | 38.51113 | 27.68389 | 27.67422 | 27.67131 |
| 63 | 108.0723 | 2.006369 | 6.2643 | 10.7568 | 4.2098 | 97.26738 | 38.09506 | 28.14301 | 26.22923 | 26.22647 |
| 64 | 93.38702 | 1.815287 | 4.4117 | 9.7608  | 3.8626 | 84.89241 | 30.40817 | 26.37295 | 20.68747 | 20.6853  |
| 65 | 120.3369 | 2.197452 | 5.966  | 10.209  | 4.4702 | 110.8296 | 41.28781 | 27.14207 | 27.22469 | 27.22183 |
| 66 | 127.1148 | 2.261146 | 6.7824 | 11.7279 | 4.7306 | 115.5962 | 45.78051 | 28.36872 | 30.46826 | 30.46506 |
| 67 | 87.09333 | 1.878981 | 5.2438 | 9.0138  | 3.7758 | 78.49051 | 28.21213 | 26.43995 | 20.92122 | 20.91902 |
| 68 | 120.3369 | 2.324841 | 5.9974 | 10.8066 | 4.2532 | 110.111  | 42.00642 | 27.61448 | 24.10174 | 24.0992  |

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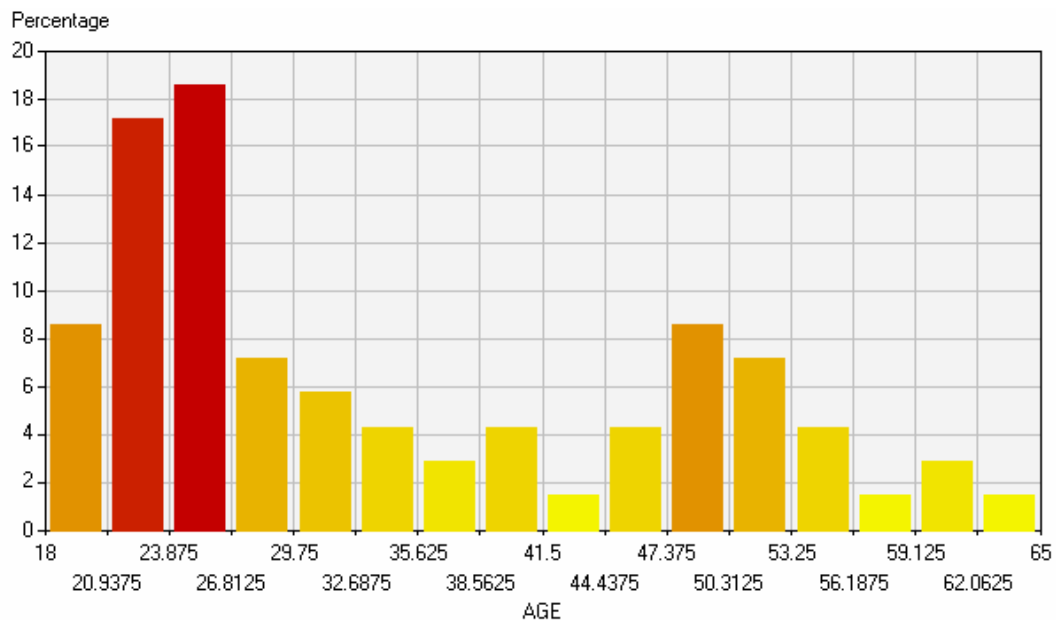
Results and Discussion

|    |          |          |        |        |        |          |          |          |          |          |
|----|----------|----------|--------|--------|--------|----------|----------|----------|----------|----------|
| 69 | 91.28913 | 1.847134 | 4.5687 | 8.8893 | 3.9494 | 83.62766 | 28.80694 | 25.62106 | 20.40358 | 20.40144 |
| 70 | 110.6543 | 1.942675 | 5.7148 | 9.9351 | 4.2098 | 101.1569 | 37.73289 | 27.1675  | 26.49548 | 26.49269 |

## CLUSTER ANALYSIS

We partitioned the complete dataset into 2 based on the participants' age (Graph: 2). We had 24 postmenopausal individuals with an age cut-off of  $>45$  in cluster1 and the remaining 46 premenopausal individuals in cluster2 (Table: 3).

### I. CLUSTERING BASED ON AGE



**GRAPH 2**

## Results and Discussion

A Study on Insulin Resistance and Obesity Among Women  
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**TABLE 3**

| CLUSTER | FREQUENCY            |
|---------|----------------------|
| 1       | 24 (Post menopausal) |
| 2       | 46                   |

| CASE ID | CLUSTER | CASE ID   | CLUSTER  |
|---------|---------|-----------|----------|
| 1       | 2       | 36        | 2        |
| 2       | 2       | 37        | 2        |
| 3       | 2       | 38        | 2        |
| 4       | 2       | 39        | 2        |
| 5       | 2       | <b>40</b> | <b>1</b> |
| 6       | 2       | 41        | 2        |
| 7       | 2       | 42        | 2        |
| 8       | 2       | 43        | 2        |
| 9       | 2       | <b>44</b> | <b>1</b> |
| 10      | 2       | <b>45</b> | <b>1</b> |
| 11      | 2       | <b>46</b> | <b>1</b> |
| 12      | 2       | 47        | 2        |

## Results and Discussion

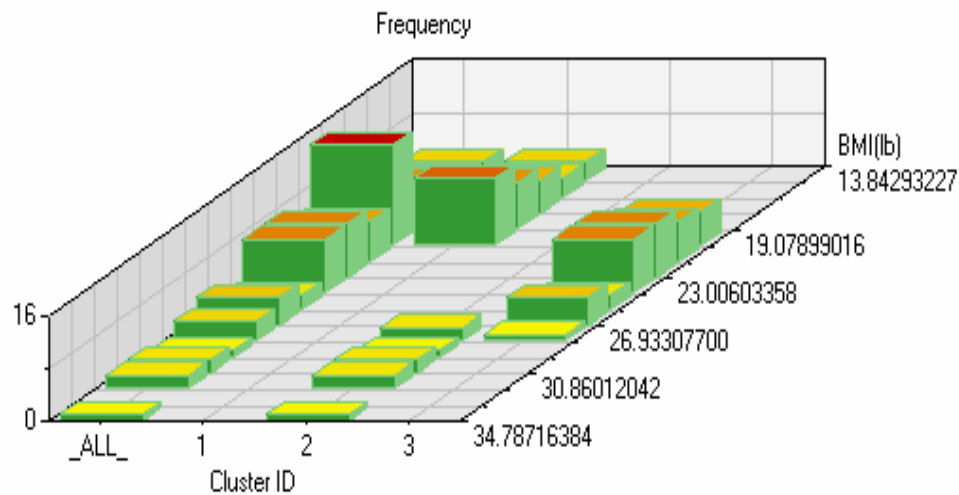
|           |          |           |          |
|-----------|----------|-----------|----------|
| 13        | 2        | 48        | 2        |
| 14        | 2        | 49        | 2        |
| 15        | 2        | <b>50</b> | <b>1</b> |
| 16        | 2        | <b>51</b> | <b>1</b> |
| 17        | 2        | <b>52</b> | <b>1</b> |
| 18        | 2        | 53        | 2        |
| 19        | 2        | <b>54</b> | <b>1</b> |
| 20        | 2        | 55        | 2        |
| <b>21</b> | <b>1</b> | <b>56</b> | <b>1</b> |
| 22        | 2        | <b>57</b> | <b>1</b> |
| 23        | 2        | <b>58</b> | <b>1</b> |
| 24        | 2        | <b>59</b> | <b>1</b> |
| 25        | 2        | <b>60</b> | <b>1</b> |
| 26        | 2        | <b>61</b> | <b>1</b> |
| 27        | 2        | <b>62</b> | <b>1</b> |
| 28        | 2        | <b>63</b> | <b>1</b> |
| 29        | 2        | <b>64</b> | <b>1</b> |
| 30        | 2        | <b>65</b> | <b>1</b> |
| 31        | 2        | <b>66</b> | <b>1</b> |

## Results and Discussion

|    |   |           |          |
|----|---|-----------|----------|
| 32 | 2 | <b>67</b> | <b>1</b> |
| 33 | 2 | 68        | 1        |
| 34 | 2 | 69        | 1        |
| 35 | 2 | 70        | 1        |

## CLUSTERING BASED ON BFM AND BMI

On clustering the total population using BFM and BMI values eight individuals were identified to be overweight/obese.



**GRAPH 3**

**TABLE 5**

| CLUSTER | FREQUENCY | CASE ID |
|---------|-----------|---------|
| 1       | 28        |         |

## Results and Discussion

|   |                  |                             |
|---|------------------|-----------------------------|
| 2 | <b>8</b> (obese) | 7,17, 21, 23, 41, 61, 62,66 |
| 3 | 34               |                             |

| S.<br>N<br>O | VARIABLES | TOTAL<br>STD | WITHIN<br>STD | R <sup>2</sup>  | RSQ/(1-<br>RSQ) |
|--------------|-----------|--------------|---------------|-----------------|-----------------|
| 1            | BFM       | 1.11900      | 0.70062       | <b>0.619349</b> | 1.627076        |
| 2            | BMI (lb)  | 4.36004      | 2.00031       | <b>0.795620</b> | 3.892849        |
| 3            | OVER-ALL  | 3.18293      | 1.49868       | 0.784727        | 3.645260        |

### CLUSTER ANALYSIS (PRE-MENOPAUSAL WOMEN)

| CASE ID | CLUSTER  | CASE ID | CLUSTER  |
|---------|----------|---------|----------|
| 1       | 1        | 36      | 3        |
| 2       | 1        | 37      | 1        |
| 3       | 3        | 38      | 1        |
| 4       | 3        | 39      | 3        |
| 5       | 1        | 40      | 1        |
| 6       | 3        | 41      | <b>2</b> |
| 7       | <b>2</b> | 42      | 3        |

## Results and Discussion

|    |          |    |          |
|----|----------|----|----------|
| 8  | 1        | 43 | 1        |
| 9  | 3        | 44 | 3        |
| 10 | 1        | 45 | 3        |
| 11 | 1        | 46 | 3        |
| 12 | 3        | 47 | 3        |
| 13 | 1        | 48 | 3        |
| 14 | 1        | 49 | 3        |
| 15 | 1        | 50 | 3        |
| 16 | 1        | 51 | 3        |
| 17 | <b>2</b> | 52 | 3        |
| 18 | 1        | 53 | 3        |
| 19 | 3        | 54 | 3        |
| 20 | 1        | 55 | 1        |
| 21 | 2        | 56 | 3        |
| 22 | 1        | 57 | 3        |
| 23 | <b>2</b> | 58 | 1        |
| 24 | 1        | 59 | 3        |
| 25 | 3        | 60 | 3        |
| 26 | 1        | 61 | <b>2</b> |

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|    |   |    |          |
|----|---|----|----------|
| 27 | 1 | 62 | <b>2</b> |
| 28 | 3 | 63 | 3        |
| 29 | 1 | 64 | 3        |
| 30 | 1 | 65 | 3        |
| 31 | 1 | 66 | <b>2</b> |
| 32 | 3 | 67 | 3        |
| 33 | 1 | 68 | 3        |
| 34 | 1 | 69 | 3        |
| 35 | 1 | 70 | 3        |

## CLUSTERING BASED ON FAT DISTRIBUTION [FWWH MEASURES]

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We further attempted to cluster the pre-menopausal women to identify the variables that has major role in body fat distribution. All four anthropometric measurements namely wrist circumference, forearm circumference, waist circumference and hip circumference were taken into account to estimate body fat distribution. We found that wrist circumference had less influence in body fat distribution while waist circumference and forearm circumference values of the subjects contributed more in defining obesity. Using the measures of body fat distribution six individuals were found to be overweight/obese.

**TABLE 7**

| <b>CLUSTER</b> | <b>FREQUENCY</b> |
|----------------|------------------|
| 1              | 22               |
| 2              | 18               |
| <b>3</b>       | <b>6</b>         |

## Results and Discussion

| S. NO | VARIABLES | TOTAL STD | WITHIN STD | R <sup>2</sup>  | RSQ/(1-RSQ) |
|-------|-----------|-----------|------------|-----------------|-------------|
| 1     | Wrist     | 0.54630   | 0.48275    | 0.253818        | 0.340156    |
| 2     | Forearm   | 0.73141   | 0.48275    | 0.618272        | 1.619664    |
| 3     | Waist     | 4.38169   | 2.19117    | <b>0.761041</b> | 3.184821    |
| 4     | Hip       | 3.39843   | 1.87467    | 0.709230        | 2.439146    |
| 5     | Over-all  | 2.80989   | 1.48007    | 0.734883        | 2.771916    |

| CASE ID | CLUSTER | CASE ID | CLUSTER |
|---------|---------|---------|---------|
| 1       | 1       | 25      | 2       |
| 2       | 1       | 26      | 1       |
| 3       | 2       | 27      | 1       |
| 4       | 1       | 28      | 2       |
| 5       | 1       | 29      | 1       |

## Results and Discussion

|    |          |    |          |
|----|----------|----|----------|
| 6  | 2        | 30 | 1        |
| 7  | <b>3</b> | 31 | 2        |
| 8  | 1        | 32 | 2        |
| 9  | <b>3</b> | 33 | 1        |
| 10 | 1        | 34 | 1        |
| 11 | 1        | 35 | 1        |
| 12 | 2        | 36 | 2        |
| 13 | 1        | 37 | 1        |
| 14 | 2        | 38 | 2        |
| 15 | 1        | 39 | 2        |
| 16 | 1        | 41 | <b>3</b> |
| 17 | <b>3</b> | 42 | 2        |
| 18 | 1        | 43 | 1        |
| 19 | 2        | 47 | 2        |
| 20 | 2        | 48 | 2        |
| 22 | 1        | 49 | 2        |
| 23 | <b>3</b> | 53 | <b>3</b> |
| 24 | 1        | 55 | 1        |

### CLUSTERING BASED ON TBW AND HEIGHT

On clustering the pre-menopausal women using two variables namely total body weight (TBW) and height we found that TBW showed good correlation co-efficient of 0.864823. Therefore, based on this cluster six subjects were identified as overweight/obese.

**TABLE 8**

| CLUSTER  | FREQUENCY |
|----------|-----------|
| 1        | 22        |
| <b>2</b> | <b>6</b>  |
| 3        | 18        |

| S. NO | VARIABLES | TOTAL STD | WITHIN STD | R <sup>2</sup>  | RSQ/(1-RSQ) |
|-------|-----------|-----------|------------|-----------------|-------------|
| 1     | TBW (lb)  | 21.69613  | 8.16029    | <b>0.864823</b> | 6.397722    |
| 2     | HEIGHT    | 2.59971   | 2.42915    | 0.165713        | 0.198628    |

## Results and Discussion

|   |          |          |         |          |          |
|---|----------|----------|---------|----------|----------|
|   | (inch)   |          |         |          |          |
| 3 | Over-all | 15.45122 | 6.02042 | 0.854928 | 5.893117 |

| CASE ID | CLUSTER  | CASE ID | CLUSTER |
|---------|----------|---------|---------|
| 1       | 1        | 25      | 3       |
| 2       | 1        | 26      | 1       |
| 3       | 3        | 27      | 1       |
| 4       | 3        | 28      | 3       |
| 5       | 1        | 29      | 1       |
| 6       | <b>2</b> | 30      | 1       |
| 7       | <b>2</b> | 31      | 1       |
| 8       | 1        | 32      | 3       |
| 9       | <b>2</b> | 33      | 1       |
| 10      | 1        | 34      | 3       |
| 11      | 3        | 35      | 1       |
| 12      | 3        | 36      | 3       |
| 13      | 1        | 37      | 1       |
| 14      | 3        | 38      | 3       |
| 15      | 1        | 39      | 3       |

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|    |          |    |          |
|----|----------|----|----------|
| 16 | 3        | 41 | <b>2</b> |
| 17 | <b>2</b> | 42 | 1        |
| 18 | 1        | 43 | 1        |
| 19 | 3        | 47 | 1        |
| 20 | 3        | 48 | 3        |
| 22 | 1        | 49 | 3        |
| 23 | <b>2</b> | 53 | 3        |
| 24 | 1        | 55 | 1        |

## CLUSTERING BASED ON ANTHROPOMETRIC MEASURES

On performing cluster analysis using all the variables namely TBW, height, wrist circumference, forearm circumference, waist circumference and hip circumference in the pre-menopausal population we found that TBW, forearm circumference and hip circumference were useful in defining obesity and six women were identified as overweight/obese.

**TABLE 9**

| CLUSTER  | FREQUENCY |
|----------|-----------|
| 1        | 22        |
| <b>2</b> | <b>6</b>  |
| 3        | 18        |

| S. NO | VARIABLES     | TOTAL STD | WITHIN STD | R <sup>2</sup> | RSQ/(1-RSQ) |
|-------|---------------|-----------|------------|----------------|-------------|
| 1     | TBW (lb)      | 21.69613  | 8.16029    | 0.864823       | 6.397722    |
| 2     | HEIGHT (inch) | 2.59971   | 2.42915    | 0.165713       | 0.198628    |
| 3     | WRIST         | 0.54630   | 0.49698    | 0.209171       | 0.264496    |
| 4     | FOREARM       | 0.73141   | 0.47063    | 0.604362       | 1.527564    |
| 5     | WAIST         | 4.38169   | 3.04949    | 0.537166       | 1.160603    |
| 6     | HIP           | 3.39843   | 1.63513    | 0.778790       | 3.520598    |
| 7     | OVER-ALL      | 9.21107   | 3.76237    | 0.840574       | 5.272508    |

| CASE ID | CLUSTER | CASE ID | CLUSTER |
|---------|---------|---------|---------|
| 1       | 1       | 25      | 3       |

## Results and Discussion

|    |          |    |          |
|----|----------|----|----------|
| 2  | 1        | 26 | 1        |
| 3  | 3        | 27 | 1        |
| 4  | 3        | 28 | 3        |
| 5  | 1        | 29 | 1        |
| 6  | 2        | 30 | 1        |
| 7  | <b>2</b> | 31 | 1        |
| 8  | 1        | 32 | 3        |
| 9  | <b>2</b> | 33 | 1        |
| 10 | 1        | 34 | 3        |
| 11 | 3        | 35 | 1        |
| 12 | 3        | 36 | 3        |
| 13 | 1        | 37 | 1        |
| 14 | 3        | 38 | 3        |
| 15 | 1        | 39 | 3        |
| 16 | 3        | 41 | <b>2</b> |
| 17 | <b>2</b> | 42 | 1        |
| 18 | 1        | 43 | 1        |
| 19 | 3        | 47 | 1        |
| 20 | 3        | 48 | 3        |



|    |          |    |          |
|----|----------|----|----------|
| 22 | 1        | 49 | 3        |
| 23 | <b>2</b> | 53 | <b>3</b> |
| 24 | 1        | 55 | 1        |

## SUMMARY OF CLUSTER ANALYSIS IN PRE-MENOPAUSAL WOMEN

**TABLE 10**

| S.<br>NO | VARIABLES   | CASE ID OF<br>OBESE SUBJECTS | NUMBER OF<br>CASES |
|----------|---|------------------------------|--------------------|
|          |   | CLUSTER                      |                    |
| 1        | Circumferences of forearm, wrist, waist and hip               | 7, 9, 17, 23, 41, 53         | 6                  |
| 2        | TBW, height, circumferences of forearm, wrist, waist and hip. | 6, 7, 9, 17, 23, 41          | 6                  |
| 3        | TBW and height  | 6, 7, 9, 17, 23, 41          | 6                  |

It is evident that the pre-menopausal women with ID no 7, 9, 17, 23 and 41 are overweight/obese from the summary of cluster analysis.

## **CLUSTER ANALYSIS IN POST-MENOPAUSAL INDIVIDUALS**

### **Clustering Based On All Anthropometric Measures**

On performing cluster analysis using all the variables namely TBW, height, wrist circumference, forearm circumference, waist circumference and hip circumference in the post-menopausal population we found that TBW, forearm circumference and hip circumference were useful in defining obesity and two women were identified as overweight/obese. Since we observed that the same parameters contributed in defining obesity in pre-menopausal population, we conclude that the above three variables are useful to stratify individuals using anthropometric measures based on cluster analysis.

## **TABLE 11**

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## Results and Discussion

| CLUSTER  | FREQUENCY |
|----------|-----------|
| <b>1</b> | <b>2</b>  |
| 2        | 12        |
| 3        | 10        |

| S. NO | VARIABLES     | TOTAL STD | WITHIN STD | R <sup>2</sup>  | RSQ/(1-RSQ) |
|-------|---------------|-----------|------------|-----------------|-------------|
| 1     | TBW (lb)      | 20.52239  | 7.46815    | <b>0.879090</b> | 7.270626    |
| 2     | HEIGHT (inch) | 2.58763   | 2.56981    | 0.099493        | 0.110486    |
| 3     | WRIST         | 0.46421   | 0.32914    | 0.540984        | 1.178571    |
| 4     | FOREARM       | 0.69092   | 0.26081    | <b>0.869895</b> | 6.686093    |
| 5     | WAIST         | 3.94593   | 2.68675    | 0.576700        | 1.362391    |
| 6     | HIP           | 3.88832   | 1.81405    | <b>0.801268</b> | 4.031907    |
| 7     | OVER-ALL      | 8.74878   | 3.48958    | 0.854741        | 5.884259    |

## Results and Discussion

| CASE ID   | CLUSTER  | CASE ID   | CLUSTER | CASE ID   | CLUSTER | CASE ID   | CLUSTER  |
|-----------|----------|-----------|---------|-----------|---------|-----------|----------|
| <b>21</b> | <b>1</b> | <b>51</b> | 3       | <b>59</b> | 2       | <b>65</b> | 3        |
| <b>40</b> | 2        | <b>52</b> | 2       | <b>60</b> | 3       | <b>66</b> | <b>1</b> |
| <b>44</b> | 2        | <b>54</b> | 2       | <b>61</b> | 3       | <b>67</b> | 2        |
| <b>45</b> | 2        | <b>56</b> | 3       | <b>62</b> | 3       | 68        | 3        |
| <b>46</b> | 2        | <b>57</b> | 3       | <b>63</b> | 3       | 69        | 2        |
| <b>50</b> | 2        | <b>58</b> | 3       | <b>64</b> | 2       | 70        | 3        |

## CLUSTERING BASED ON FAT DISTRIBUTION (FWWH MEASURES)

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When we attempted to cluster the post-menopausal population based on fat distribution measures we were able to identify the variable that has major role in body fat distribution. All four anthropometric measurements namely wrist circumference, forearm circumference, waist circumference and hip circumference were taken into account to estimate body fat distribution. We found that only waist circumference and hip circumference values of the subjects contributed much in defining obesity. Using the measures of body fat distribution three individuals were found to be overweight/obese.

**TABLE 12**

| CLUSTER | FREQUENCY       |
|---------|-----------------|
| 1       | 3 (Obese)       |
| 2       | 7               |
| 3       | 14 (overweight) |

| S.<br>NO | VARIABLES | TOTAL<br>STD | WITHIN<br>STD | R <sup>2</sup> | RSQ/(1-<br>RSQ) |
|----------|-----------|--------------|---------------|----------------|-----------------|
|----------|-----------|--------------|---------------|----------------|-----------------|

## Results and Discussion

|   |          |         |         |                 |          |
|---|----------|---------|---------|-----------------|----------|
| 1 | WRIST    | 0.46421 | 0.31146 | 0.588975        | 1.432942 |
| 2 | FOREARM  | 0.69092 | 0.47158 | 0.574643        | 1.350969 |
| 3 | WAIST    | 3.94593 | 2.05934 | <b>0.751315</b> | 3.021144 |
| 4 | HIP      | 3.88832 | 2.16595 | <b>0.716689</b> | 2.529690 |
| 5 | OVER-ALL | 2.80099 | 1.52082 | 0.730831        | 2.715136 |

| CASE ID   | CLUSTER  | CASE ID   | CLUSTER | CASE ID   | CLUSTER  | CASE ID   | CLUSTER  |
|-----------|----------|-----------|---------|-----------|----------|-----------|----------|
| <b>21</b> | <b>1</b> | <b>51</b> | 3       | <b>59</b> | 3        | <b>65</b> | 3        |
| <b>40</b> | 2        | <b>52</b> | 3       | <b>60</b> | 3        | <b>66</b> | <b>1</b> |
| <b>44</b> | 3        | <b>54</b> | 2       | <b>61</b> | <b>1</b> | <b>67</b> | 2        |
| <b>45</b> | 3        | <b>56</b> | 3       | <b>62</b> | 3        | 68        | 3        |
| <b>46</b> | 2        | <b>57</b> | 3       | <b>63</b> | 3        | 69        | 2        |
| <b>50</b> | 3        | <b>58</b> | 2       | <b>64</b> | 2        | 70        | 3        |

### CLUSTERING BASED ON TBW AND HEIGHT

On clustering the post-menopausal women using two variables namely total body weight (TBW) and height we found that TBW showed good correlation co-efficient

of 0.914734. Therefore, based on this cluster four subjects were identified as overweight/obese.

**TABLE 13**

| CLUSTER | FREQUENCY      |
|---------|----------------|
| 1       | 4 (Obese)      |
| 2       | 12             |
| 3       | 8 (overweight) |

## Results and Discussion

| S. NO | VARIABLES     | TOTAL STD | WITHIN STD | R <sup>2</sup>  | RSQ/(1-RSQ) |
|-------|---------------|-----------|------------|-----------------|-------------|
| 1     | TBW (lb)      | 20.52239  | 6.27150    | <b>0.914734</b> | 10.727945   |
| 2     | HEIGHT (inch) | 2.58763   | 2.52542    | 0.130332        | 0.149864    |
| 3     | OVER-ALL      | 14.62642  | 4.78066    | 0.902458        | 9.252004    |

| CASE ID   | CLUSTER | CASE ID   | CLUSTER | CASE ID   | CLUSTER | CASE ID   | CLUSTER |
|-----------|---------|-----------|---------|-----------|---------|-----------|---------|
| <b>21</b> | 1       | <b>51</b> | 3       | <b>59</b> | 2       | <b>65</b> | 1       |
| <b>40</b> | 2       | <b>52</b> | 2       | <b>60</b> | 3       | <b>66</b> | 1       |
| <b>44</b> | 2       | <b>54</b> | 2       | <b>61</b> | 3       | <b>67</b> | 2       |
| <b>45</b> | 2       | <b>56</b> | 3       | <b>62</b> | 3       | 68        | 1       |
| <b>46</b> | 2       | <b>57</b> | 3       | <b>63</b> | 3       | 69        | 2       |
| <b>50</b> | 2       | <b>58</b> | 2       | <b>64</b> | 2       | 70        | 3       |

## CLUSTERING BASED ON WAIST AND HIP CIRCUMFERENCE



Since we found that both waist circumference and hip circumference contributed in body fat distribution we attempted to stratify individuals based on these two variables and identified that three subjects fall under overweight/obese category.

**TABLE 14**

| CLUSTER | FREQUENCY |
|---------|-----------|
| 1       | 3         |
| 2       | 7         |
| 3       | 14        |

| S.<br>NO | VARIABLES | TOTAL<br>STD | WITHIN<br>STD | R <sup>2</sup> | RSQ/(1-<br>RSQ) |
|----------|-----------|--------------|---------------|----------------|-----------------|
|----------|-----------|--------------|---------------|----------------|-----------------|

|   |          |         |         |          |          |
|---|----------|---------|---------|----------|----------|
| 1 | WAIST    | 3.94593 | 2.05934 | 0.751315 | 3.021144 |
| 2 | HIP      | 3.88832 | 2.16595 | 0.716689 | 2.529690 |
| 3 | OVER-ALL | 3.91723 | 2.11332 | 0.734256 | 2.763025 |

### CLUSTERING BASED ON WAIST CIRCUMFERENCE

Cluster analysis of the post-menopausal population based on waist circumference clearly stratified the subjects into three groups and we found that five individuals were obese.

**TABLE 15**

| CLUSTER | FREQUENCY   |
|---------|-------------|
| 1       | 5 (obese)   |
| 2       | 2 (lean)    |
| 3       | 17 (normal) |

## Results and Discussion

| S. NO | VARIABLES | TOTAL STD | WITHIN STD | R <sup>2</sup>  | RSQ/(1-RSQ) |
|-------|-----------|-----------|------------|-----------------|-------------|
| 1     | WAIST     | 3.94593   | 1.83838    | <b>0.801818</b> | 4.045860    |
| 2     | OVER-ALL  | 3.94593   | 1.83838    | 0.801818        | 4.045860    |

| CASE ID   | CLUSTER  | CASE ID   | CLUSTER | CASE ID   | CLUSTER  | CASE ID   | CLUSTER  |
|-----------|----------|-----------|---------|-----------|----------|-----------|----------|
| <b>21</b> | <b>1</b> | <b>51</b> | 3       | <b>59</b> | 3        | <b>65</b> | 3        |
| <b>40</b> | 3        | <b>52</b> | 3       | <b>60</b> | <b>1</b> | <b>66</b> | <b>1</b> |
| <b>44</b> | 3        | <b>54</b> | 3       | <b>61</b> | <b>1</b> | <b>67</b> | 3        |
| <b>45</b> | 3        | <b>56</b> | 3       | <b>62</b> | 3        | 68        | 3        |
| <b>46</b> | 3        | <b>57</b> | 3       | <b>63</b> | <b>1</b> | 69        | 2        |
| <b>50</b> | 3        | <b>58</b> | 3       | <b>64</b> | 2        | 70        | 3        |

## SUMMARY OF CLUSTER ANALYSIS IN POST-MENOPAUSAL WOMEN

**TABLE 16**

| S.NO | VARIABLES                                      | CASE ID OF OBESE SUBJECTS | NUMBER OF CASES |
|------|--|---------------------------|-----------------|
|      |  | CLUSTER                   |                 |
| 1    | TBW, height, circumferences of wrist, forearm, | 21, 66                    | 2               |

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|   |   |                    |   |
|---|---|--------------------|---|
|   | waist and hip.                                  |                    |   |
| 2 | Circumferences of forearm, wrist, waist and hip | 21, 61, 66         | 3 |
| 3 | TBW and height                                  | 21, 61, 66, 68     | 4 |
| 4 | Circumferences of, waist and hip                | 21, 61, 66         | 3 |
| 5 | Waist circumference                             | 21, 60, 61, 63, 66 | 5 |

It is evident that the post-menopausal women with ID no 21, 61, and 66 are overweight/obese from the summary of cluster analysis.

## **HORMONAL PARAMETERS ALTERED IN OBESE BREAST CANCER PATIENTS**

We attempted to identify the hormonal parameters that are significantly altered in obese breast cancer patients from the reported data (McTiernan *et al.* 2003) in order to exploit them as screening markers along with body mass index (BMI) and body fat mass (BFM).

We found the levels of estradiol ( $E_2$ ), (free estradiol  $FE_2$ ), dehydroepiandrosterone (DHEAS), estrone ( $E_1$ ), testosterone (T) and free testosterone (FT) were significantly elevated except with sex hormone-binding globulin (SHBG).

REPORTED DATA OF SEX HORMONES IN OBESE BREAST CANCER PATIENTS (McTiernan *et al.* 2003)

**Table: 17**

**HORMONAL PARAMETERS THAT ARE SIGNIFICANTLY ALTERED IN OBESE BREAST CANCER PATIENTS**

| S.NO | CATEGORY | TYPE   | E <sub>2</sub> | F E <sub>2</sub> | DHEAS | E <sub>1</sub> | SHBG | T     | FT  |
|------|----------|--------|----------------|------------------|-------|----------------|------|-------|-----|
| 1 a. | BMI      | LIGHT  | 4.7            | 0.1              | 50.5  | 19.7           | 73.9 | 94.5  | 2.1 |
| b    | BMI      | NORMAL | 8.3            | 0.18             | 53.2  | 22.3           | 66.2 | 118.1 | 2.9 |
| c    | BMI      | M OWT  | 8              | 0.2              | 55.6  | 21.2           | 52.1 | 127.4 | 4   |
| d    | BMI      | S OWT  | 10.6           | 0.28             | 60    | 22.7           | 43.4 | 126   | 4.6 |

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|      |     |         |      |      |      |      |      |       |     |
|------|-----|---------|------|------|------|------|------|-------|-----|
| e    | BMI | OBESE   | 10.7 | 0.28 | 59.3 | 26.5 | 38.1 | 176.5 | 7.6 |
| II.a | BFM | LIGHT   | 6.6  | 0.14 | 48.4 | 19.9 | 73.6 | 99.9  | 2.2 |
| b    | BFM | NORMAL  | 6.4  | 0.13 | 55.1 | 21.2 | 62.5 | 112.5 | 2.8 |
| c    | BFM | OVER WT | 5.8  | 0.14 | 55   | 20.7 | 49.7 | 132.1 | 4.1 |
| d    | BFM | OBESE   | 12.2 | 0.35 | 57.3 | 26.1 | 38.4 | 168.6 | 7.2 |

**TABLE 18**

| S.NO | METH | TYPE | $\frac{T}{SHBG}$ | T/FT | SHBG/T | $\frac{SHBG}{F E2}$ | $\frac{SHBG}{E2}$ | $\frac{E}{FE2}$ | $\frac{E1}{E2}$ | $\frac{E2}{F E2}$ | E2/T | EST*<br>E2 | E2*<br>F E2 | FE2*<br>10 |
|------|------|------|------------------|------|--------|---------------------|-------------------|-----------------|-----------------|-------------------|------|------------|-------------|------------|
|------|------|------|------------------|------|--------|---------------------|-------------------|-----------------|-----------------|-------------------|------|------------|-------------|------------|

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# Results and Discussion

|      |     |        |      |      |        |       |       |       |        |       |        |       |       |     |
|------|-----|--------|------|------|--------|-------|-------|-------|--------|-------|--------|-------|-------|-----|
| I a. | BMI | LIGHT  | 1.28 | 45   | 0.782  | 73.9  | 15.72 | 47    | 92.59  | 47    | 0.0497 | 92.59 | 0.47  | 1   |
| b    | BMI | NORMAL | 1.78 | 40.7 | 0.5605 | 36.78 | 7.98  | 46.11 | 185.09 | 46.11 | 0.0703 | 185.1 | 1.49  | 1.8 |
| c    | BMI | M OWT  | 2.45 | 31.9 | 0.4089 | 26.05 | 6.51  | 40    | 169.6  | 40    | 0.0628 | 169.6 | 1.6   | 2   |
| d    | BMI | S OWT  | 2.9  | 27.4 | 0.3444 | 15.5  | 4.094 | 37.86 | 240.62 | 37.86 | 0.0841 | 240.6 | 2.968 | 2.8 |
| e    | BMI | OBESE  | 4.63 | 23.2 | 0.2159 | 13.61 | 3.56  | 38.21 | 283.55 | 38.21 | 0.0606 | 283.6 | 2.996 | 2.8 |
| II.a | BFM | LIGHT  | 1.36 | 45.4 | 0.7367 | 52.57 | 11.15 | 47.14 | 3.02   | 47.14 | 0.0661 | 131.3 | 0.924 | 1.4 |
| b    | BFM | NORMAL | 1.8  | 40.2 | 0.5556 | 48.08 | 9.77  | 49.23 | 3.31   | 49.23 | 0.0569 | 135.7 | 0.83  | 1.3 |
| c    | BFM | OVERWT | 2.66 | 32.2 | 0.3762 | 35.5  | 8.57  | 41.43 | 3.57   | 41.43 | 0.0439 | 120.1 | 0.812 | 1.4 |
| d    | BFM | OBESE  | 4.39 | 23.4 | 0.2278 | 10.97 | 3.15  | 34.86 | 2.14   | 34.86 | 0.0724 | 318.4 | 4.27  | 3.5 |

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## CALCULATION OF PERCENTAGE SHIFT USING REPORTED DATA

**TABLE 19**

| S.NO | PARAMETERS | OBESE BREAST CANCER PATIENTS |        |       |        |        |              |        |        |        | % SHIFT FROM |              |
|------|------------|------------------------------|--------|-------|--------|--------|--------------|--------|--------|--------|--------------|--------------|
|      |            | BASED ON BMI                 |        |       |        |        | BASED ON BFM |        |        |        | OVERWEIGHT   |              |
|      |            | LIGHT                        | N      | M.OVT | S.OVT  | OBESE  | LIGHT        | N      | OVERWT | OBESE  | BMI          | BFM          |
| 1    | T          | 94.5                         | 118.1  | 127.4 | 126    | 176.5  | 99.9         | 112.5  | 132.1  | 168.6  | <b>28.61</b> | 21.65        |
| 2    | FT         | 2.1                          | 2.9    | 4     | 4.6    | 7.6    | 2.2          | 2.8    | 4.1    | 7.2    | <b>39.47</b> | 43.06        |
| 3    | T/SHBG     | 1.28                         | 1.78   | 2.45  | 2.9    | 4.63   | 1.36         | 1.8    | 2.66   | 4.39   | <b>37.36</b> | 39.41        |
| 4    | E1 x E2    | 92.59                        | 185.09 | 169.6 | 240.62 | 283.55 | 131.34       | 135.68 | 120.06 | 318.42 | 15.14        | <b>62.29</b> |
| 5    | E2 x FE2   | 0.47                         | 1.49   | 1.6   | 2.968  | 2.996  | 0.924        | 0.83   | 0.812  | 4.27   | 0.935        | <b>80.98</b> |
| 6    | SHBG/E2    | 15.72                        | 7.98   | 6.51  | 4.094  | 3.56   | 11.15        | 9.77   | 8.57   | 3.15   | 13.04        | <b>63.24</b> |

Therefore the anthropometric measures of postmenopausal women are important for the breast cancer risk prediction.

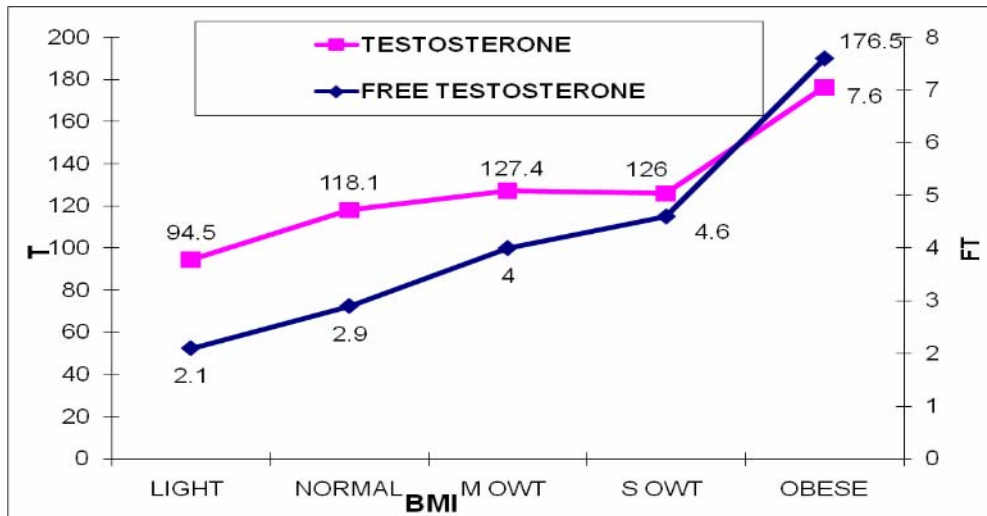
## Results and Discussion

A Study on Insulin Resistance and Obesity Among Women at High Risk for Breast Cancer  
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## GRAPHS USING REPORTED HORMONAL PARAMETERS

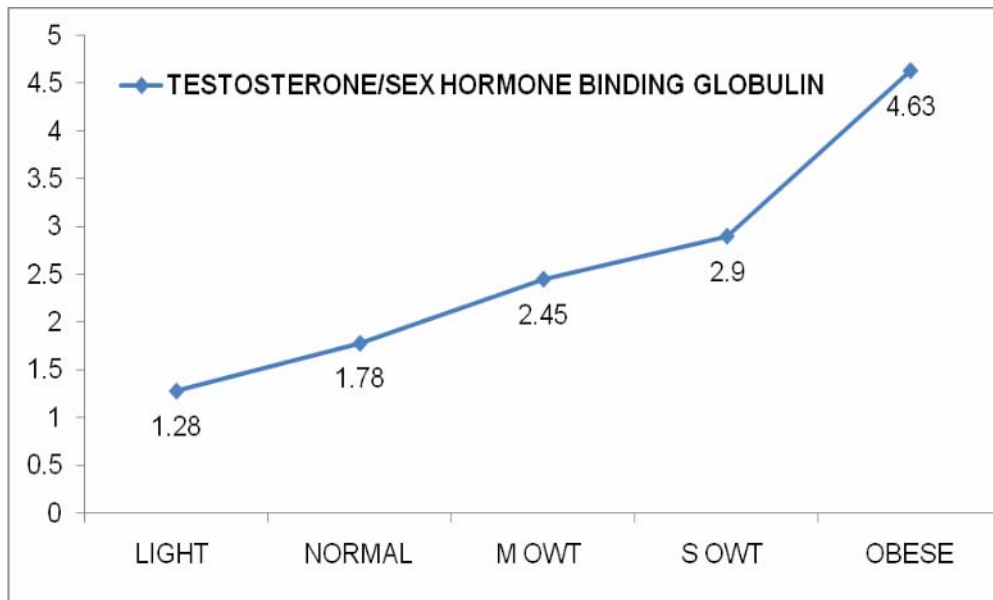
### GRAPH: 4

#### TESTOSTERONE AND FREE TESTOSTERONE (BMI)



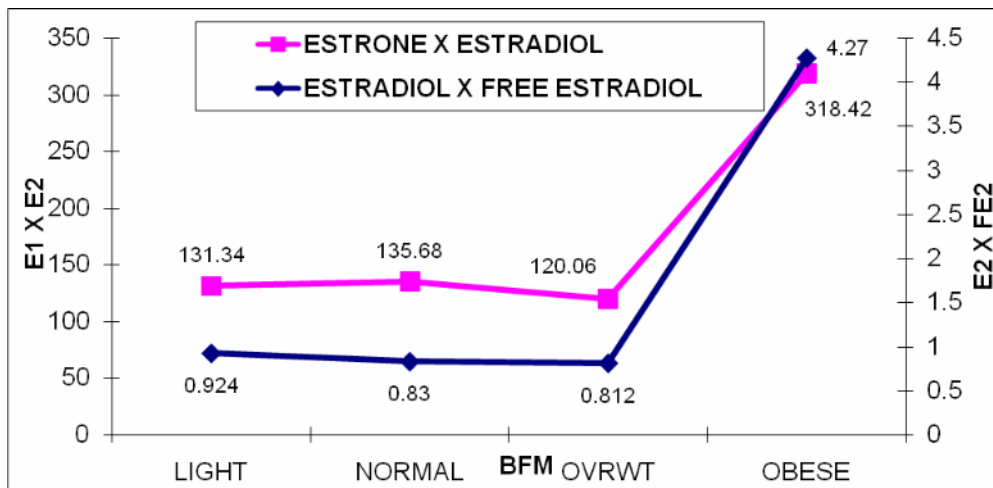
### GRAPH 5

#### RATIO OF T/SHBG (BMI)



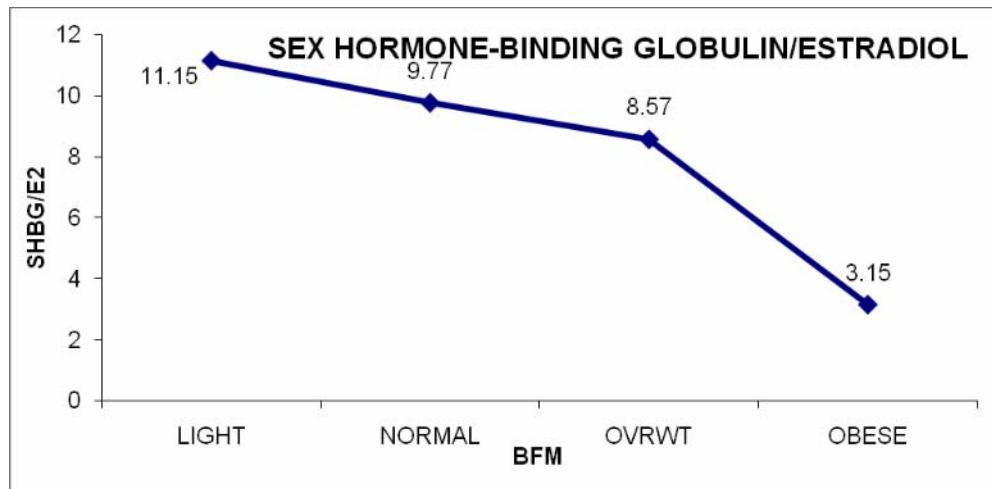
## PRODUCTS OF TOTAL AND BIOAVAILABLE ESTROGENS

GRAPH 6



## RATIO OF SHBG AND ESTRADIOL (BFM)

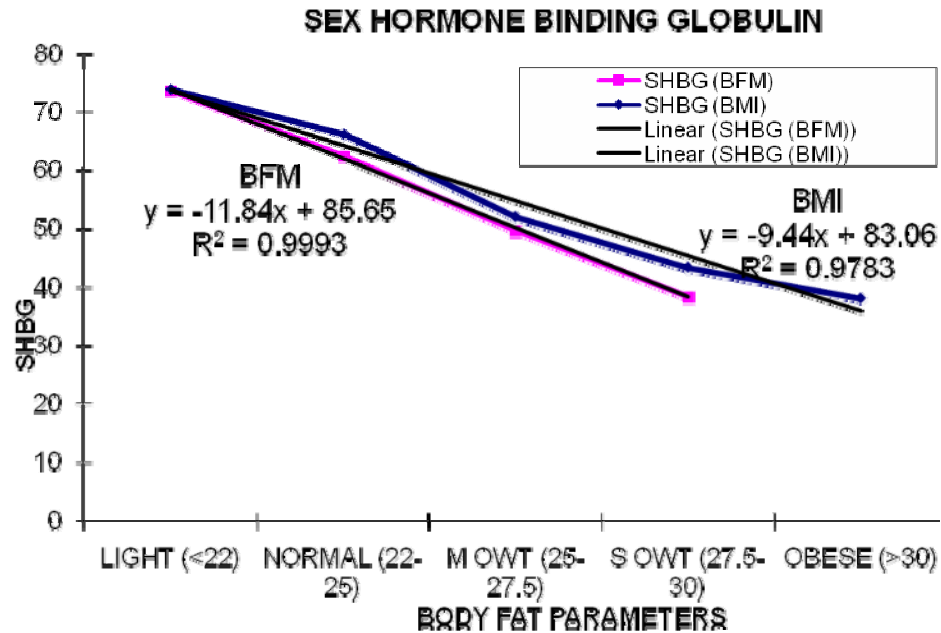
A Study on Insulin Resistance and Obesity among Women at High Risk for Breast Cancer using Cluster Analysis

**GRAPH 7**

With the percentage shift values (Table: 19) and from the graphs (4-7) it is evident that obese postmenopausal individuals with elevated estradiol ( $E_2$ ), (free estradiol  $FE_2$ ), and estrone ( $E_1$ ), should be evaluated based on their BFM values for assessing their breast cancer risk. The ratio of sex hormone-binding globulin to estradiol value is found to be declining among obese individuals.

**SHBG AS A GENERALIZED BODY WEIGHT MARKER****GRAPH 8**

A Study on Insulin Resistance and Obesity among Women at High Risk for Breast Cancer using Cluster Analysis



The sex hormone-binding globulin values are showing a strong linear negative correlation with body weight across all categories of breast cancer patients. As this observation is also seen in normal individuals, SHBG can be considered as a general marker for obesity.

## DATA OF 29 HEALTHY FEMALE INDIVIDUALS

TABLE 20

| ANTH CASE ID | CASE ID    | STATUS    | AGE | HT IN INCH | TBW IN LB | WRIST | FOREARM | WAIST | HIP  |
|--------------|------------|-----------|-----|------------|-----------|-------|---------|-------|------|
| 9G           | <b>51</b>  |           | 25  | 62.992     | 145.5036  | 6.1   | 9.6     | 40.8  | 42.3 |
| 13G          | <b>81</b>  |           | 25  | 62.2046    | 94.7978   | 5.4   | 8       | 28    | 35   |
| 77GN         | <b>131</b> |           | 24  | 62.5983    | 141.0944  | 6     | 9       | 34.2  | 38   |
| 72GN         | <b>2</b>   |           | 24  | 67.3227    | 169.7542  | 6.4   | 11      | 38    | 42   |
| 11G          | <b>71</b>  | <b>FH</b> | 24  | 64.5668    | 108.0254  | 5.6   | 8.2     | 27    | 34.9 |
| 3G           | <b>181</b> | <b>FH</b> | 24  | 62.00775   | 121.253   | 6     | 9       | 31    | 38.3 |
| 12GG         | 62         |           | 24  | 104.7242   | 123.4576  | 5.9   | 9       | 30    | 39.3 |
| 79GNN        | <b>122</b> | <b>FH</b> | 24  | 62.992     | 116.8438  | 5.5   | 9.2     | 32    | 37.4 |
| 79GN         | <b>121</b> | <b>FH</b> | 24  | 62.992     | 116.8438  | 5.5   | 9.2     | 32    | 37.4 |



## Results and Discussion

|      |            |           |    |          |          |     |      |      |      |
|------|------------|-----------|----|----------|----------|-----|------|------|------|
| 2G   | <b>171</b> | <b>FH</b> | 25 | 57.95264 | 92.5932  | 5.5 | 8.4  | 31.8 | 33.5 |
| 2GG  | <b>172</b> | <b>FH</b> | 25 | 57.95264 | 92.5932  | 5.5 | 8.4  | 31.8 | 33.5 |
| 11GG | <b>72</b>  | <b>FH</b> | 24 | 103.9368 | 110.23   | 5.6 | 8.2  | 27   | 34.9 |
| 82GN | <b>21</b>  | <b>FH</b> | 27 | 63.3857  | 154.322  | 7   | 10   | 35   | 40   |
| 71GN | <b>14</b>  |           | 24 | 61.4172  | 108.0254 | 5.8 | 9    | 28   | 34   |
| 19G  | <b>19</b>  |           | 30 | 67.3227  | 169.7542 | 6.4 | 11   | 38   | 42   |
| 74GN | 1          |           | 24 | 61.0235  | 101.4116 | 5.9 | 8.2  | 28.4 | 35   |
| 9GG  | 52         |           | 25 | 62.992   | 145.5036 | 6.1 | 9.6  | 40.8 | 42.3 |
| 5G   | 16         |           | 24 | 60.15736 | 102.5139 | 6.1 | 9.1  | 29   | 35.1 |
| 4G   | 4          |           | 24 | 65.55105 | 134.4806 | 6   | 8.9  | 35.2 | 41   |
| 76GN | 10         |           | 24 | 61.8109  | 121.253  | 6   | 9.5  | 29   | 37.4 |
| 80GN | 9          |           | 25 | 64.9605  | 165.345  | 6   | 9.5  | 35   | 43   |
| 75GN | 15         |           | 24 | 61.0235  | 154.322  | 6   | 10.3 | 32   | 38   |

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|       |           |  |    |          |          |     |   |      |      |
|-------|-----------|--|----|----------|----------|-----|---|------|------|
| 73GN  | 3         |  | 24 | 65.15735 | 125.6622 | 6   | 9 | 31   | 36   |
| 13GG  | <b>82</b> |  | 25 | 62.2046  | 94.7978  | 5.4 | 8 | 28   | 35   |
| 77GNN | 132       |  | 24 | 62.5983  | 141.0944 | 6   | 9 | 34.2 | 38   |
| 81GN  | 20        |  | 25 | 63.3857  | 116.8438 | 6   | 9 | 34   | 37   |
| 78GN  | 11        |  | 24 | 64.36995 | 99.207   | 6   | 8 | 26   | 35   |
| 3GG   | 182       |  | 24 | 62.00775 | 121.253  | 6   | 9 | 31   | 38.3 |
| 12G   | <b>61</b> |  | 24 | 65.3542  | 121.253  | 5.9 | 9 | 30   | 39.3 |

### CALCULATION OF BMI AND BFM OF 29 PREMENOPAUSAL WOMEN

**TABLE 21**

| ANTH CASE ID | CASE ID   | STATUS | AGE | LBM      | BFW      | BFM      | BMI(lb)  |
|--------------|-----------|--------|-----|----------|----------|----------|----------|
| 9G           | <b>51</b> |        | 25  | 104.6664 | 40.83719 | 28.0661  | 25.77854 |
| 13G          | <b>81</b> |        | 25  | 70.45973 | 24.33807 | 25.67366 | 17.22299 |

## Results and Discussion

|       |            |           |    |          |          |          |          |
|-------|------------|-----------|----|----------|----------|----------|----------|
| 77GN  | <b>131</b> |           | 24 | 103.2535 | 37.84087 | 26.81954 | 25.31279 |
| 72GN  | <b>2</b>   |           | 24 | 123.6353 | 46.11891 | 27.16805 | 26.33012 |
| 11G   | <b>71</b>  | <b>FH</b> | 24 | 80.47473 | 27.55067 | 25.50388 | 18.21641 |
| 3G    | <b>181</b> | <b>FH</b> | 24 | 89.15732 | 32.09568 | 26.47001 | 22.1695  |
| 12GG  | 62         |           | 24 | 90.64724 | 32.81036 | 26.57621 | 7.91369  |
| 79GNN | <b>122</b> | <b>FH</b> | 24 | 85.92445 | 30.91935 | 26.46212 | 20.70095 |
| 79GN  | <b>121</b> | <b>FH</b> | 24 | 85.92445 | 30.91935 | 26.46212 | 20.70095 |
| 2G    | <b>171</b> | <b>FH</b> | 25 | 68.82831 | 23.76489 | 25.66591 | 19.38153 |
| 2GG   | <b>172</b> | <b>FH</b> | 25 | 68.82831 | 23.76489 | 25.66591 | 19.38153 |
| 11GG  | <b>72</b>  | <b>FH</b> | 24 | 82.0885  | 28.1415  | 25.5298  | 7.173258 |
| 82GN  | <b>21</b>  | <b>FH</b> | 27 | 113.065  | 41.257   | 26.73436 | 27.00229 |
| 71GN  | <b>14</b>  |           | 24 | 80.95273 | 27.07267 | 25.0614  | 20.13266 |
| 19G   | <b>19</b>  |           | 30 | 123.6353 | 46.11891 | 27.16805 | 26.33012 |

## Results and Discussion

|       |           |  |    |          |          |          |          |
|-------|-----------|--|----|----------|----------|----------|----------|
| 74GN  | 1         |  | 24 | 75.48427 | 25.92733 | 25.56643 | 19.14471 |
| 9GG   | 52        |  | 25 | 104.6664 | 40.83719 | 28.0661  | 25.77854 |
| 5G    | 16        |  | 24 | 76.62635 | 25.88755 | 25.25272 | 19.91409 |
| 4G    | 4         |  | 24 | 97.46483 | 37.01577 | 27.52499 | 22.00167 |
| 76GN  | 10        |  | 24 | 89.91242 | 31.34058 | 25.84726 | 22.31093 |
| 80GN  | 9         |  | 25 | 119.8514 | 45.49363 | 27.51437 | 27.54531 |
| 75GN  | 15        |  | 24 | 113.8457 | 40.47627 | 26.22845 | 29.13325 |
| 73GN  | 3         |  | 24 | 92.95756 | 32.70464 | 26.02584 | 20.80814 |
| 13GG  | <b>82</b> |  | 25 | 70.45973 | 24.33807 | 25.67366 | 17.22299 |
| 77GNN | 132       |  | 24 | 103.2535 | 37.84087 | 26.81954 | 25.31279 |
| 81GN  | 20        |  | 25 | 85.78249 | 31.06131 | 26.58362 | 20.44459 |
| 78GN  | 11        |  | 24 | 74.19235 | 25.01465 | 25.2146  | 16.83183 |
| 3GG   | 182       |  | 24 | 89.15732 | 32.09568 | 26.47001 | 22.1695  |

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|     |           |  |    |          |          |          |          |
|-----|-----------|--|----|----------|----------|----------|----------|
| 12G | <b>61</b> |  | 24 | 89.03348 | 32.21952 | 26.57215 | 19.95726 |
|-----|-----------|--|----|----------|----------|----------|----------|

## ORAL GLUCOSE TOLERANCE TEST (OGTT) AND INSULIN ASSAY VALUES

**TABLE 22**

| `1`   | CASE ID    | STATUS    | AGE | 0MIN       | 30MIN      | 60MIN      | 90MIN      | 120MIN     | INS<br>0MIN | INS<br>30MIN | INS<br>120MIN |
|-------|------------|-----------|-----|------------|------------|------------|------------|------------|-------------|--------------|---------------|
| 9G    | <b>51</b>  |           | 25  | <b>94</b>  | <b>131</b> | <b>84</b>  | <b>75</b>  | <b>83</b>  | <b>3.7</b>  | <b>66.7</b>  | <b>2.2</b>    |
| 13G   | <b>81</b>  |           | 25  | <b>91</b>  | <b>96</b>  | <b>68</b>  | <b>70</b>  | <b>89</b>  |             | <b>53.4</b>  |               |
| 77GN  | <b>131</b> |           | 24  | <b>81</b>  | <b>115</b> | <b>139</b> | <b>126</b> | <b>79</b>  |             | <b>52.6</b>  |               |
| 72GN  | <b>2</b>   |           | 24  | <b>59</b>  | <b>135</b> | <b>111</b> | <b>86</b>  | <b>77</b>  | 6.4         | 53.6         | 12.5          |
| 11G   | <b>71</b>  | <b>FH</b> | 24  | <b>104</b> | <b>118</b> | <b>159</b> | <b>116</b> | <b>103</b> |             | <b>33.2</b>  |               |
| 3G    | <b>181</b> | <b>FH</b> | 24  | <b>103</b> | <b>156</b> | <b>147</b> | <b>110</b> | <b>98</b>  |             | <b>29</b>    |               |
| 12GG  | 62         |           | 24  | 90         | 133        | 112        | 70         | 93         | 3.1         | 17.2         | 2.8           |
| 79GNN | <b>122</b> | <b>FH</b> | 24  | <b>78</b>  | <b>159</b> | <b>178</b> | <b>148</b> | <b>125</b> |             |              |               |

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## Results and Discussion

|      |            |           |    |            |            |            |            |            |  |  |  |
|------|------------|-----------|----|------------|------------|------------|------------|------------|--|--|--|
| 79GN | <b>121</b> | <b>FH</b> | 24 | <b>75</b>  | <b>161</b> | <b>176</b> | <b>148</b> | <b>129</b> |  |  |  |
| 2G   | <b>171</b> | <b>FH</b> | 25 | <b>81</b>  | <b>166</b> | <b>176</b> | <b>119</b> | <b>70</b>  |  |  |  |
| 2GG  | <b>172</b> | <b>FH</b> | 25 | <b>83</b>  | <b>151</b> | <b>175</b> | <b>119</b> | <b>75</b>  |  |  |  |
| 11GG | <b>72</b>  | <b>FH</b> | 24 | <b>105</b> | <b>133</b> | <b>154</b> | <b>138</b> | <b>89</b>  |  |  |  |
| 82GN | <b>21</b>  | <b>FH</b> | 27 | <b>98</b>  | <b>110</b> | <b>140</b> | <b>129</b> | <b>88</b>  |  |  |  |
| 71GN | <b>14</b>  |           | 24 | <b>65</b>  | <b>133</b> | <b>134</b> | <b>109</b> | <b>74</b>  |  |  |  |
| 19G  | <b>19</b>  |           | 30 | <b>98</b>  | <b>147</b> | <b>132</b> | <b>114</b> | <b>100</b> |  |  |  |
| 74GN | 1          |           | 24 | 77         | 133        | 124        | 93         | 82         |  |  |  |
| 9GG  | 52         |           | 25 | 94         | 137        | 124        | 104        | 95         |  |  |  |
| 5G   | 16         |           | 24 | 109        | 137        | 123        | 109        | 98         |  |  |  |
| 4G   | 4          |           | 24 | 87         | 147        | 122        | 111        | 84         |  |  |  |
| 76GN | 10         |           | 24 | 91         | 131        | 119        | 96         | 105        |  |  |  |
| 80GN | 9          |           | 25 | 81         | 141        | 118        | 96         | 85         |  |  |  |

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|       |           |  |    |           |            |            |            |           |  |  |  |
|-------|-----------|--|----|-----------|------------|------------|------------|-----------|--|--|--|
| 75GN  | 15        |  | 24 | 88        | 131        | 117        | 102        | 89        |  |  |  |
| 73GN  | 3         |  | 24 | 88        | 131        | 115        | 91         | 84        |  |  |  |
| 13GG  | <b>82</b> |  | 25 | <b>94</b> | <b>156</b> | <b>115</b> | <b>100</b> | <b>93</b> |  |  |  |
| 77GNN | 132       |  | 24 | 87        | 128        | 115        | 97         | 107       |  |  |  |
| 81GN  | 20        |  | 25 | 80        | 137        | 114        | 105        | 96        |  |  |  |
| 78GN  | 11        |  | 24 | 97        | 136        | 113        | 100        | 68        |  |  |  |
| 3GG   | 182       |  | 24 | 101       | 133        | 111        | 111        | 98        |  |  |  |
| 12G   | <b>61</b> |  | 24 | <b>93</b> | <b>104</b> | <b>98</b>  | <b>60</b>  | <b>94</b> |  |  |  |

## CALCULATION OF INSULIN SENSITIVITY & INSULIN SECRETION INDICES:

**TABLE 23**

| CASE ID   | ANTH CASE ID | HOMA2 %B | HOMA2 %S | HOMA2 IR | HOMA2 %B30 | HOMA2 %S30 | HOMA2 IR30 | log IR | 1/LOG IR | log IR30 | 1/LOG IR30 |
|-----------|--------------|----------|----------|----------|------------|------------|------------|--------|----------|----------|------------|
| <b>51</b> | 9G           | 53.3     | 204      | 0.5      | -          | -          | -          | -0.301 | -3.322   |          |            |

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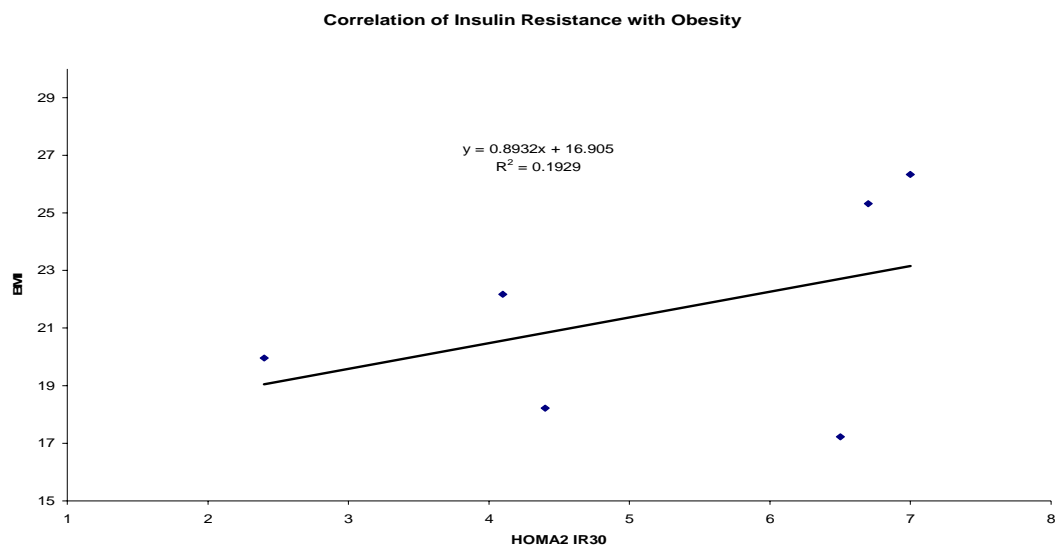
|            |      |       |     |     |             |             |            |        |        |        |         |
|------------|------|-------|-----|-----|-------------|-------------|------------|--------|--------|--------|---------|
| <b>81</b>  | 13G  |       |     |     | 316         | 15.4        | 6.5        |        |        | 0.8129 | 1.23014 |
| <b>131</b> | 77GN |       |     |     | <b>227</b>  | <b>15</b>   | <b>6.7</b> |        |        | 0.8261 | 1.21054 |
| <b>2</b>   | 72GN | 197.6 | 136 | 0.7 | 176         | 14.2        | 7          | -0.155 | -6.456 | 0.8451 | 1.1833  |
| <b>71</b>  | 11G  |       |     |     | <b>156</b>  | <b>22.8</b> | <b>4.4</b> |        |        | 0.6435 | 1.55412 |
| <b>181</b> | 3G   |       |     |     | <b>86.6</b> | <b>24.4</b> | <b>4.1</b> |        |        | 0.6128 | 1.6319  |
| 62         | 12GG | 51.8  | 246 | 0.4 | 78.2        | 41.6        | 2.4        | -0.398 | -2.513 | 0.3802 | 2.63012 |

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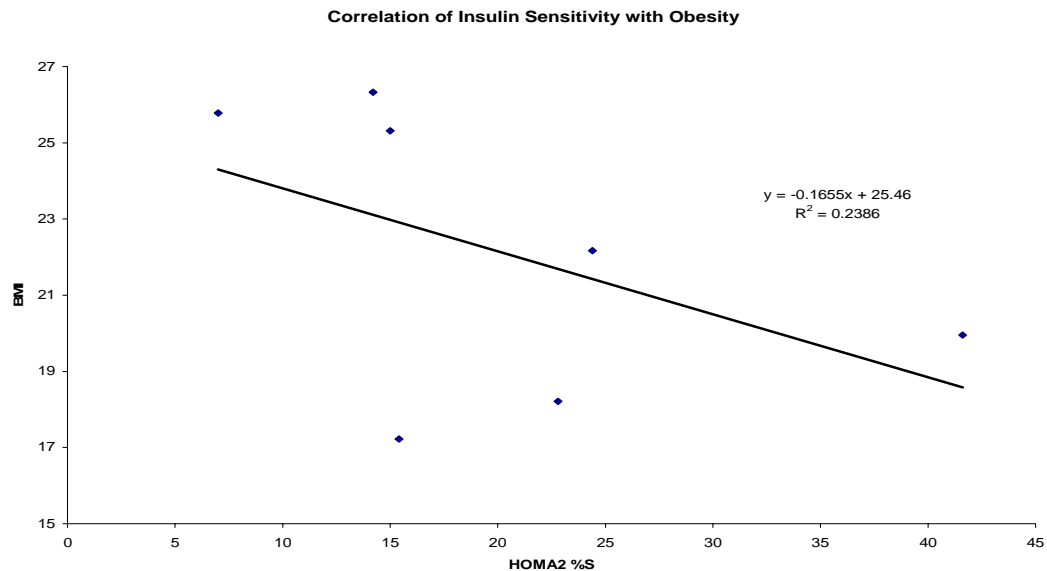


## GRAPHS DEMONSTRATING THE RELATIONSHIP BETWEEN INSULIN RESISTANCE WITH OBESITY

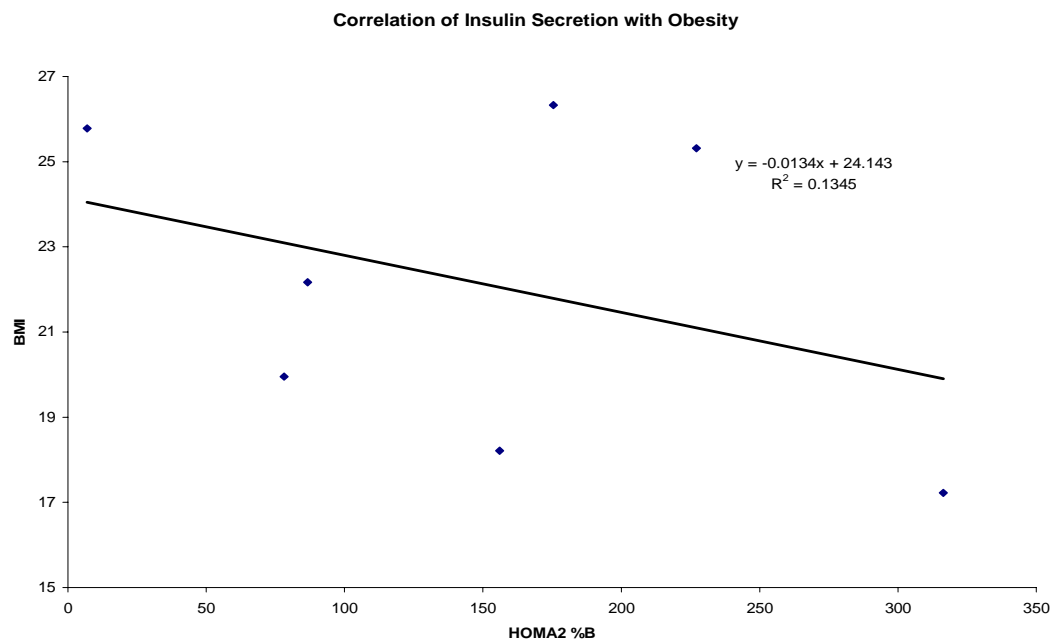
**GRAPH 9**



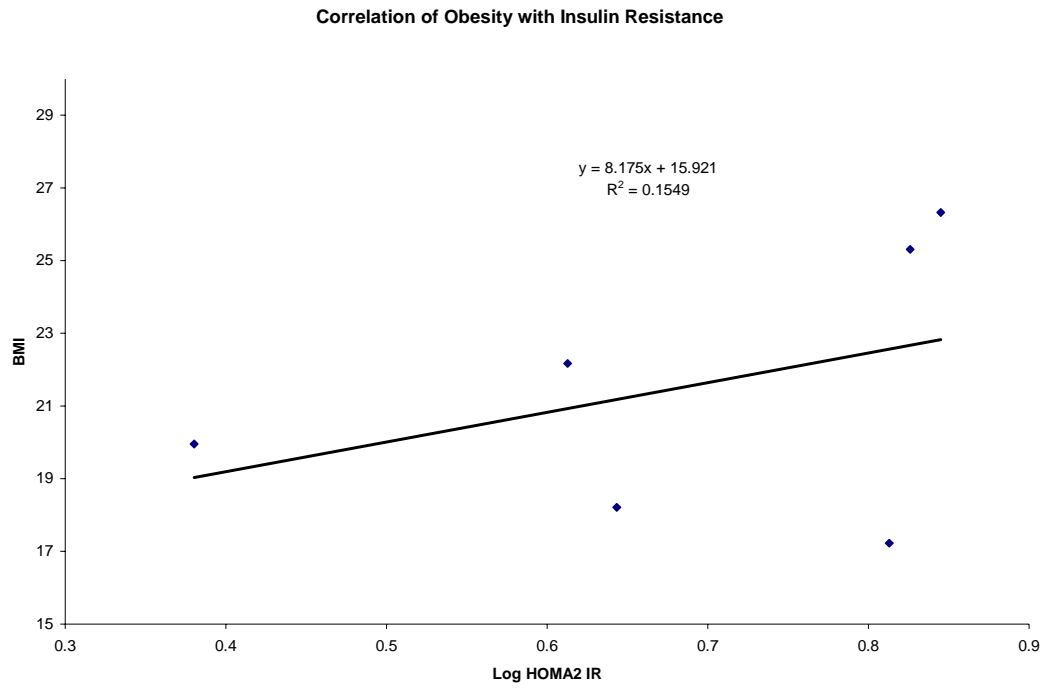
**GRAPH 10**



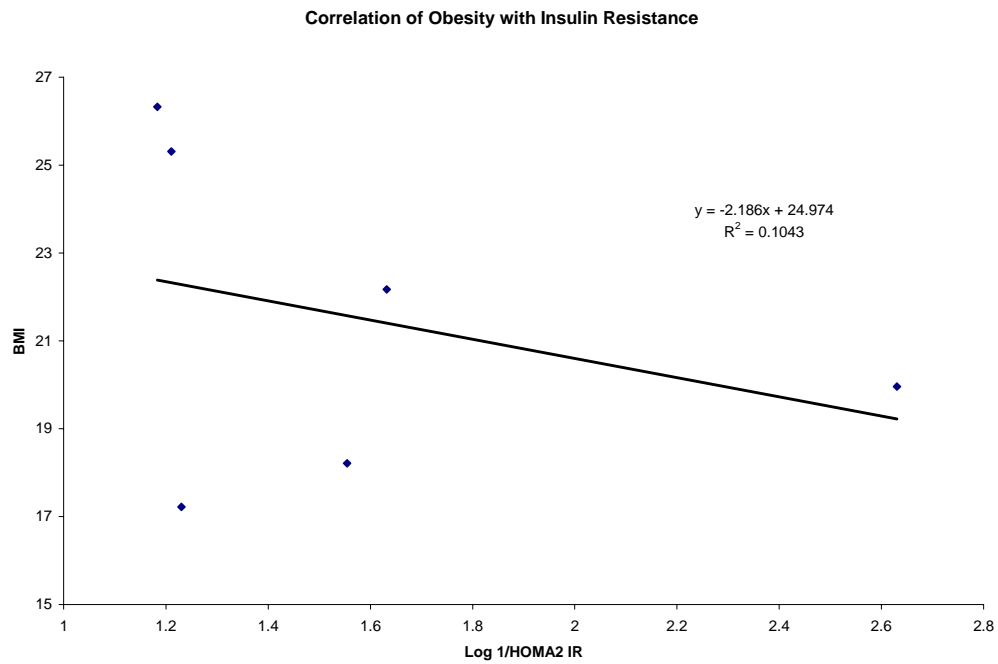
**GRAPH 11**



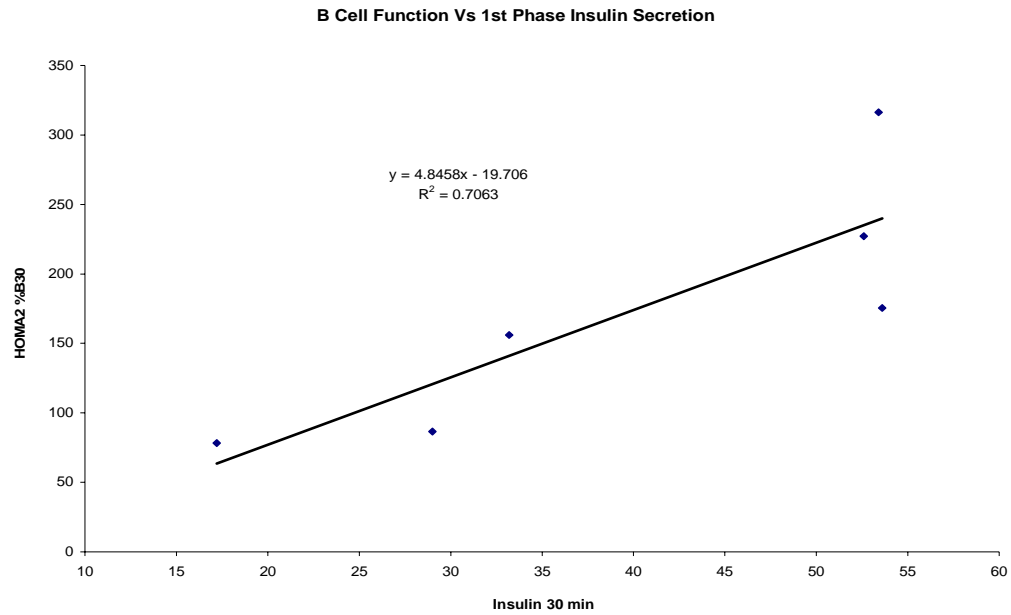
**GRAPH 12**



**GRAPH 13**

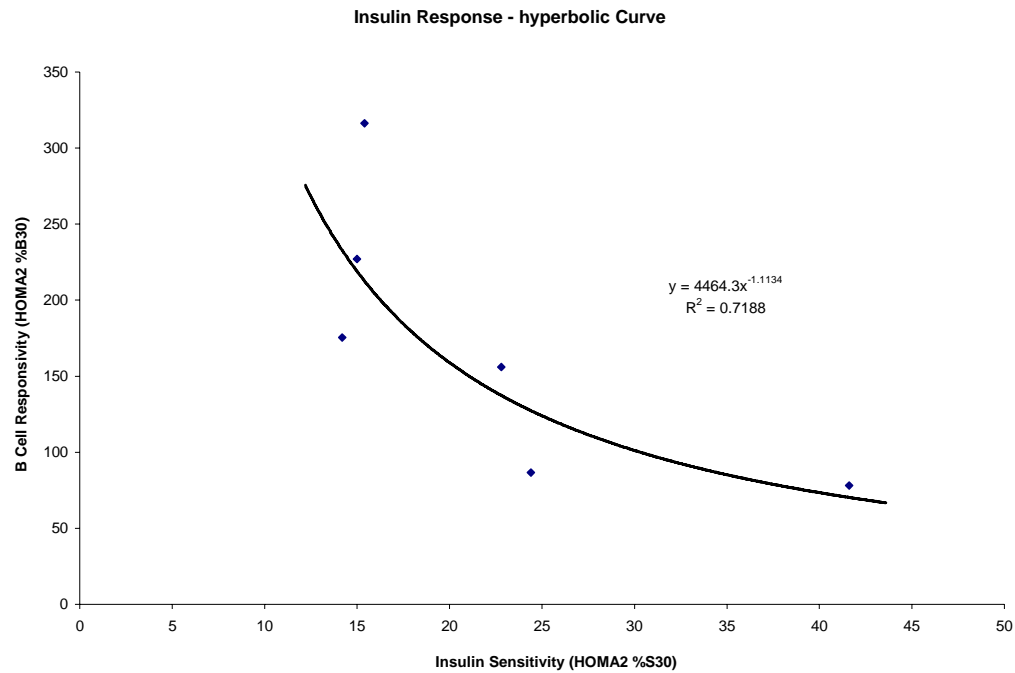


## GRAPH 14



## GRAPH 15

A Study on Insulin Resistance and Obesity among Women  
at High Risk for Breast Cancer using Cluster Analysis



We have correlated the obesity marker BMI with the indices of oral glucose tolerance test (OGTT) surrogate measures of insulin response to demonstrate only a weak, positive correlation between insulin resistance and obesity. This could be due to the relatively small number of subjects included in the study. However, when BMI values were plotted against insulin resistance indices (HOMA 2 IR and log HOMA 2 IR) a weak, positive correlation was observed (graph 9 and 12) while it was plotted against insulin sensitivity indices HOMA 2% S, a weak, linear, negative correlation was observed). This is consistent with the principle of insulin resistance and insulin

sensitivity as they are inversely related to each other. Similarly, when BMI was plotted against  $\log 1/\text{HOMA 2 IR}$  as well as  $\text{HOMA 2\% B}$  we observed a weak, linear negative correlation (graph 10, 11 and 13). When the values of index of  $\beta$ -cell responsivity,  $\text{HOMA 2\% B}$  is plotted against the index of first phase insulin secretion, insulin 30 minutes a good strong, linear, positive correlation is observed (graph:14). This is expected as both the indices represent insulin release. A hyperbolic-like relationship was observed between insulin sensitivity and insulin secretion when  $\text{HOMA 2\% B}$  values were plotted against  $\text{HOMA 2\% S}$  values (graph: 15). Generally such a relationship (between insulin sensitivity and insulin secretion) is used to understand the nature of type-2 diabetes. Glucose tolerance is bad if an individual is located below the hyperbolic line, drawn from OGTT values of NGT individuals. Glucose tolerance is good if an individual is located on or above that line.

**QUESTIONNAIRE DEVELOPED USING EXISTING MODELS**

|               |   |    |                   |   |    |
|---------------|---|----|-------------------|---|----|
| Gail Model    | - | G  | Shattuck – Eidens | - |    |
| SE            |   |    |                   |   |    |
| Claus Model   | - | CL | Couch             | - | Co |
| BRCAPRO       | - | BR | Frank             | - | FR |
| Cuzick- Tyrer | - | CT | Rosner & Colditz  | - | RC |
| BOADICEA      | - | BO | Gilpin            | - | GI |
| FORD          | - | F  | Evans             | - | EV |

1. What is the woman's age? (ALL)
2. How many of the woman's FDR-mother, sisters, daughters, father or sons have been diagnosed with breast cancer? (ALL)
3. How many of the woman's SDR- grand parents, grand children, aunt, uncle, niece or nephew have been diagnosed with breast cancer? (CL, BR, CT, BO, F, GI, EV)
4. How many of the woman's TDR have been diagnosed with breast cancer? (BO, GI, EV)
5. If your relatives have had breast cancer, what was the age of onset of the disease ? (CL, BR, CT, BO, F, GI, EV)
  - a. Age of onset- <55 (Co)
  - b. Age of onset- <50 (FR)
6. Have any of your relatives been diagnosed with bilateral breast cancer? (BR, CT, BO, F, SE, FR)
  - a. Bilateral/multifocal breast tumors (GI, EV)
7. Have any of your relatives been diagnosed with ovarian cancer? (BR, CT, BO, F, SE, FR, GI, EV)



8. Have any of your male relatives been diagnosed with breast cancer? (BR, BO, F, GI, EV)
9. Have any of your relatives been diagnosed with both breast and ovarian cancer? (FR, GI, SE, Co)
10. Have any of your relatives been diagnosed with prostate cancer? (GI, EV)
  - a. Colon cancer (GI)
  - b. Pancreatic cancer (EV)
11. How old were you when you had your first menstrual period? (G, CT, RC)
12. How old were you when you first gave birth? (G, CT)
13. How old were you when your menstrual periods stopped (menopause)? (RC, CT)
14. Why did your menstrual periods stop? (RC)
  - a. Natural menopause
  - b. Surgery

15. Have you ever taken hormone replacement therapy? (CT, RCS)
16. Has a physician ever removed tissue from your breast (breast biopsy)? (C, GT)
17. Have you ever been diagnosed with any other breast diseases- atypical ductal hyperplasia? (G, CT)
  - a. Lobular carcinoma in situ (CT)

## QUESTIONNAIRE FOR BREAST CANCER RISK PREDICTION

### I. BASED ON PERSONAL HISTORY

1. How old were you when you had your first menstrual period?

☐  $> 12$

☐  $\leq 12$

2. a. Are you still having periods?

☐ Yes (Pre-menopausal stage)

☐ No (Post-menopausal stage)

b. Age of menopause?

☐  $\geq 45$

☐  $\leq 44$

3. a. How old were you when you first gave birth?

☐  $\geq 30$

☐  $< 29$

☐ No children

b. How many times have you given birth?

☐ 1

☐  $\geq 2$

c. Duration of breast feeding

☐ upto 6 months

☐  $> 6$  months

4. Did you experience any of the following during your pregnancy period?

☐ Frequency of nausea/ vomiting

☐ Induced abortion

☐ Spontaneous abortion

☐ Premature birth

☐ Gestational diabetes mellitus

- ☐ Excessive abnormal weight gain
- ☐ Pre-eclampsia
- ☐ Increased birth-weight

5. Any previous exposure to radiation?

- ☐ Yes
- ☐ No

a. Cause of exposure : X-ray - ☐

b. How many times? ☐

6. Have you ever had any other types of cancer?

- ☐ Ovarian cancer
- ☐ Pancreatic cancer
- ☐ Atypical Ductal Hyperplasia
- ☐ Atypical Lobular Hyperplasia
- ☐ Lobular Carcinoma in Situ

7. What is the nature of your job?

- ☐ Chemical industry
- ☐ Laboratories
- ☐ others. Please mention \_\_\_\_\_

## II. **BASED ON FAMILY HISTORY**

1. Are you adopted?

- ☐ Yes
- ☐ No

2. Have any of your blood relatives been diagnosed with breast cancer?

- ☐ No
- ☐ Mother
- ☐ Sisters
- ☐ Daughters
- ☐ Aunt
- ☐ Grandmothers

☐ Others. Please mention \_\_\_\_\_.

3. Have any of your blood relatives been diagnosed with ovarian cancer?

☐ No

☐ Mother

☐ Sisters

☐ Daughters

☐ Aunt

☐ Grandmothers

☐ Others. Please mention \_\_\_\_\_.

4. Have you observed any common genetic defects among your family members?

☐ Deaf

☐ Blind

- ☐ Dumb
- ☐ Colour blindness
- ☐ Other defects. Please mention \_\_\_\_\_.

### III. BASED ON MEASURABLE PARAMETERS

1. What is your height?

\_\_\_\_\_ m.

2. What is your body weight?

\_\_\_\_\_ kg.

3. What is your wrist circumference?

\_\_\_\_\_ cm

4. What is your forearm circumference?

\_\_\_\_\_ cm



5. What is your waist circumference?

\_\_\_\_\_ cm

6. What is your hip circumference?

\_\_\_\_\_ cm

**Body Mass Index** \_\_\_\_\_.

**Body Fat Mass** \_\_\_\_\_.

- ☐ High risk-overweight/obese
- ☐ Normal
- ☐ Underweight

#### **IV. BASED ON HORMONE DOMINANCE SYMPTOMS**

A Study on Insulin Resistance and Obesity among Women  
at High Risk for Breast Cancer using Cluster Analysis

| SYMPTOMS               | E | T | DHEA | P | SHBG |
|------------------------|---|---|------|---|------|
| Acne                   |   | T | D    |   | S    |
| Anxiety                |   | T |      | P |      |
| Bloating               | E |   |      |   |      |
| Bone loss              |   |   |      | P |      |
| Breast cyst            | E |   |      |   |      |
| Cold hands and feet    | E |   |      |   |      |
| Cyclical headaches     |   |   |      | P |      |
| Depression             | E |   |      |   |      |
| Dry eyes               | E |   |      |   |      |
| Early miscarriage      |   |   |      | P |      |
| Elevated insulin       |   |   |      |   | S    |
| Elevated triglycerides |   | T |      |   |      |
| Excess facial hair     |   | T |      |   |      |
| Fatigue                | E |   |      | P |      |
| Fibrocystic breasts    |   |   |      | P |      |
| Fibroids               |   |   |      | P |      |
| Fluid retention        |   |   |      | P |      |
| Greasy hair            |   |   | D    |   |      |

|                                 |   |   |   |   |   |
|---------------------------------|---|---|---|---|---|
| Greasy skin                     |   |   | D |   |   |
| Hair growth on face and abdomen |   |   | D |   |   |
| Hair loss                       | E |   |   | P |   |
| Heavy menstruation              | E |   |   |   |   |
| Hirsutism                       |   |   |   |   | S |
| Increased blood clot            | E |   |   |   |   |
| Inferility                      | E | T |   | P |   |
| Insomnia                        |   |   |   | P |   |
| Irritability                    | E | T |   | P |   |
| Joint pain                      |   |   |   | P |   |
| Loss of scalp hair              |   | T |   |   |   |
| Loss of Zn                      | E |   |   |   |   |
| Low body temperature            |   |   |   | P |   |
| Low libido                      | E |   |   |   |   |
| Low total cholesterol           | E |   |   |   |   |
| Menstrual cramps                | E |   |   | P |   |
| Mid-cycle pain                  |   | T |   |   |   |
| Mood swings                     | E |   |   |   |   |
| Nausea                          | E |   |   |   |   |
| Nervous                         | E | T |   |   |   |

|                                 |   |   |  |   |   |
|---------------------------------|---|---|--|---|---|
| Oily skin                       |   | T |  |   |   |
| Ovarian cysts                   |   | T |  | P |   |
| Poor sleep patterns             | E |   |  |   |   |
| Retention of Cu                 | E |   |  |   |   |
| Sleep disturbances              |   | T |  |   |   |
| Sugar cravings                  | E |   |  |   |   |
| Thinning hair on head           |   | T |  |   |   |
| Torn, weak or relaxed ligaments | E |   |  |   |   |
| Unstable blood sugar            |   | T |  |   |   |
| Vaginal dryness                 |   |   |  | P |   |
| Weight gain                     | E |   |  |   | S |
| Weight gain around abdomen      |   |   |  | P |   |

**VI. BASED ON HORMONE LEVELS**

| S.NO | PARAMETERS          | HORMONE CUTOFF POINTS<br>(MORE THAN) |        |
|------|---------------------|--------------------------------------|--------|
|      |                     | BMI                                  | BFM    |
| 1    | T                   | 126                                  | 132.1  |
| 2    | FT                  | 4.6                                  | 4.1    |
| 3    | T/SHBG              | 2.9                                  | 2.66   |
| 4    | E1 x E2             | 240.62                               | 120.06 |
| 5    | E2 x FE2            | 2.968                                | 0.812  |
| 6    | SHBG/E2 (less than) | 4.094                                | 8.57   |

**VI. BASED ON HORMONE LEVELS**

| S.NO | PARAMETERS | HORMONE CUTOFF POINTS<br>(MORE THAN) |        |
|------|------------|--------------------------------------|--------|
|      |            | BMI                                  | BFM    |
| 1    | T          | 126                                  | 132.1  |
| 2    | FT         | 4.6                                  | 4.1    |
| 3    | T/SHBG     | 2.9                                  | 2.66   |
| 4    | E1 x E2    | 240.62                               | 120.06 |

|   |                     |       |       |
|---|---------------------|-------|-------|
| 5 | E2 x FE2            | 2.968 | 0.812 |
| 6 | SHBG/E2 (less than) | 4.094 | 8.57  |

## VI. MAMMOGRAM SCREENING

The findings of different questionnaire are pooled together along with mammogram findings and then evaluated with appropriate weightage to the factors, and then the risk for breast cancer can be predicted. We hope that this can be extended for mass screening and identification of obese post-menopausal women at high risk for breast cancer.

## CONCLUSION

Obesity is a chronic disease which has spread all over the world and threatens public global health.

Obesity in postmenopausal women was highly correlated with several disorders including type 2 diabetes mellitus, hypertension, coronary heart disease, arthritis, sleep apnea, and certain forms of obesity-related cancers, including breast, prostate, endometrium, colon and gallbladder cancer. However, defining an individual as overweight/obese using widely employed markers is a complex task. Cut-off points of these markers widely vary among the different sections of women population. In order to define obesity on a local level we stratified the female population based on their anthropometric measures using cluster analysis. We also clustered them based on their body fat distribution. Thus, we could identify through an alternative approach, the obese women who may be at high risk for breast cancer.

Insulin resistance (IR) is increasingly being recognized as an important pathophysiological determinant of not only diabetes but also a number of other clinical states. We carried out oral glucose tolerance test (OGTT-glucose/insulin) with 29 healthy female individuals for exploring relationship between surrogate markers of insulin resistance and demographic parameters (BMI, BW, age). We also attempted to demonstrate the hyperbolic relationship between insulin sensitivity and  $\beta$ -cell responsitivity.

On analyzing the association between adiposity (using body mass index (BMI) and body fat mass (BFM)) and concentrations of estrogens, androgens and sex hormone-binding globulin we identified the hormonal parameters that are significantly altered in obese breast cancer patients. Thus, these biomarkers may be useful for weight loss intervention in women with breast cancer.

Since breast cancer is the most common form of cancer affecting women a comprehensive questionnaire was built using several variables and the symptoms associated with hormonal variations in the disease. We have attempted to include all the known risk factors



(personal history, family history and other measurable parameters) in a single questionnaire in order to predict the risk of breast cancer with an emphasis on hormone based screening.

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